

# A review of adverse cutaneous drug reactions resulting from the use of interferon and ribavirin

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Drug-induced cutaneous eruptions are named among the most common side effects of many medications. Thus, cutaneous drug eruptions are a common cause of morbidity and mortality, especially in hospital settings. The present article reviews different presentations of drug-induced cutaneous eruptions, with a focus on eruptions reported secondary to the use of interferon and ribavirin. Presentations include injection site reactions, psoriasis, eczematous drug reactions, alopecia, sarcoidosis, lupus, fixed drug eruptions, pigmentary changes and lichenoid eruptions. Also reviewed are findings regarding life-threatening systemic drug reactions.

**Key Words:** *Cutaneous; Drug; Eruption; Interferon; Ribavirin*

## OVERVIEW OF DRUG ERUPTIONS

An adverse drug reaction has been defined as a noxious or unintended reaction to a medication that has been administered in standard doses by the appropriate route for the purpose of prophylaxis, diagnosis or treatment (1). The prevalence of adverse cutaneous drug reactions is considerable, with drug-induced eruptions named among the most common side effects of many medications (1). Thus, adverse cutaneous drug reactions are a common cause of morbidity and mortality, particularly in hospital settings. The Boston Collaborative Drug Surveillance Program (2) collected data regarding adverse events in 15,438 consecutive medical inpatients between 1975 and 1982, and found 358 reactions in 347 patients, corresponding to an overall cutaneous drug reaction rate of 2.2%.

Reactions to medications may be immediate, accelerated (occurring within three days) or late (occurring three or more days after first receiving the drug) (1). Cutaneous reactions are generally late reactions (1). The dose and the nature of the medication account for only part of the development of a drug eruption. Age, sex, immune status and genetic make-up of the individual strongly determine the risk for the development of an adverse reaction to a medication (3). Numerous mechanisms have been implicated; however, in general, the mechanisms remain unknown (1). That being said, it is believed that approximately 10% of drug-induced rashes are the result of true allergic mechanisms, which are classified according to Coombs' types I to IV (1).

Adverse drug reactions can present on the skin in many different ways. Therefore, it is often difficult to discern merely by the morphological presentation whether an eruption is due to

## Une analyse des réactions médicamenteuses cutanées indésirables résultant de l'utilisation d'interféron et de ribavirine

Les éruptions cutanées induites par les médicaments font partie des principaux effets secondaires de nombreux médicaments. C'est pourquoi elles sont souvent responsables de morbidité et de mortalité, notamment en milieu hospitalier. Le présent article analyse diverses présentations d'éruptions cutanées médicamenteuses et s'attarde aux éruptions déclarées après l'utilisation d'interféron et de ribavirine. Les présentations incluaient des réactions au foyer d'injection, un psoriasis, des réactions eczémateuses médicamenteuses, une alopecie, une sarcoïdose, un lupus, une éruption fixe d'origine médicamenteuse, des modifications pigmentaires et des éruptions lichénoides. On y analyse également les constatations portant sur les réactions médicamenteuses systémiques mettant la vie en danger.

a medication. A high level of suspicion should be aroused by a history of symmetric eruptions that appear suddenly. This clinical picture, in conjunction with a history of either a new drug started within the preceding six weeks or a drug that has been used intermittently, is strong evidence of an adverse cutaneous drug reaction.

Table 1 outlines the clinical presentations of various adverse cutaneous drug reactions and lists many of the commonly implicated drugs. It is important to acknowledge that these morphological presentations can be accounted for with factors other than drugs. For example, liver disease, in particular hepatitis C, is associated with lichen planus independent of medication use (4). Therefore, it is imperative to correlate the physical findings with the clinical history to help establish the possible causal relationships.

As a rule, any drug that is administered systemically can cause a cutaneous eruption. Most drug eruptions are accounted for by simple exanthems and urticaria, which in one study accounted for 95% and 5% of skin reactions, respectively (2). However, drug eruptions are not limited to these common and relatively benign conditions. Adverse cutaneous drug eruptions may be part of a systemic reaction that can be life-threatening. These severe reactions accounted for only approximately 2% of all adverse cutaneous reactions (5).

Early diagnosis leads to a better outcome; therefore, it is important for every physician to be aware of the clinical features of a severe cutaneous drug reaction. A serious reaction is portended by the presence of bullae, erosions, purpura or exfoliative dermatitis. Other cutaneous features that warn of a potentially severe reaction include involvement of the mucous

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**TABLE 1**  
**Adverse cutaneous drug eruptions: Morphological presentations and commonly implicated drugs.**

Clinical presentation	Morphology of lesions	Implicated drugs
Exanthematous eruptions	Symmetrically arranged erythematous macules and papules, typically starting on the trunk and spreading peripherally	Penicillins, cephalosporins, sulfonamides, anticonvulsants, antiretrovirals
Urticaria	Pruritic, transient, edematous erythematous wheals	Penicillin and other antibiotics, opioids, acetylsalicylic acid
Pustular eruptions	Multiple pustules, or an acneiform eruption that can affect atypical areas (eg, extremities)	Glucocorticoids, isoniazid, lithium, phenytoin (acneiform); beta-lactam and macrolide antibiotics, calcium channel blockers (non-acneiform)
Bullous eruptions	Erythema, skin fragility, blister formation and scarring	Vancomycin, captopril, furosemide, penicillin, penicillamine, tetracyclines
Fixed drug eruption	A solitary, round violaceous patch evolving into an edematous plaque and resolving with pigmentation; commonly on the genitalia or perineum	Ibuprofen, naproxen, sulfonamides, tetracyclines
Skin necrosis	Red, painful plaques in fatty areas (breasts, buttocks, hips) that blister, ulcerate or develop necrosis	Coumadin and heparin (unfractionated and low molecular weight)
Lichenoid eruptions	Scaly, purplish macules and patches evolving into polygonal papules and plaques	Beta-blockers, captopril, thiazides, gold, penicillamine
Cutaneous pseudolymphoma	Solitary or widespread violaceous papules, plaques or nodules	Anticonvulsants, antidepressants, antihistamines
Vasculitis	Palpable purpura generally found on the lower extremities	Propylthiouracil, hydralazine, granulocyte colony-stimulating factor, granulocyte monocyte colony-stimulating factor, allopurinol, cefaclor, minocycline, penicillamine, phenytoin, isotretinoin

membranes, facial swelling and skin tenderness. Systemic symptoms and signs such as fever, lymphadenopathy and arthritis are also strong indicators of a severe reaction that has the potential to include drug-induced hepatitis, nephritis or the involvement of other internal organs (6). In these clinical scenarios, it is vital that the offending agent be identified and discontinued.

Two uncommon but severe drug reactions include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These are life-threatening reactions that lie on a continuum, with mortality rates reaching 30% (5). As such, it is imperative that clinicians be able to promptly recognize and institute treatment for these severe eruptions.

SJS and TEN are both bullous drug reactions that represent parts of a disease spectrum. SJS is characterized by targetoid skin lesions that induce erosion of less than 10% of the body surface area (BSA). TEN is characterized by more than 30% BSA erosion. Any percentage of BSA erosion between 10% and 30% is deemed SJS-TEN overlap syndrome. The skin lesions initially present as erythematous macules with epidermal necrosis or purpura at the centres. Any lateral pressure on the intact skin can cause further detachment of the epidermis, a phenomenon known as Nikolsky's sign. Mucous membranes are involved in approximately 90% of cases with the clinical finding of painful erosions (7).

Treatment involves the immediate withdrawal of the offending drug and the institution of supportive care, ideally in an intensive care unit or a burn unit for individuals more severely affected. This multidisciplinary approach is a key factor in minimizing the morbidity and mortality associated with these two conditions.

### CUTANEOUS REACTIONS TO INTERFERON AND RIBAVIRIN

The use of interferon has been implicated in a variety of cutaneous eruptions. The incidence of cutaneous eruptions has been estimated to be 13% to 23% (8,9). Combination therapy

with ribavirin has been associated with an increased incidence of adverse cutaneous reactions (10). For the present review, a MEDLINE search was conducted for articles published from January 2000 to August 2008, under the headings "interferon/adverse effects" or "ribavirin/adverse effects". This search yielded 2599 results. These 2599 results were then manually reviewed for studies detailing dermatological findings.

#### Injection site reaction

Localized reactions near injection sites are very common, and are estimated to occur to some degree in the majority of patients treated with interferon (11). The typical clinical presentation is an ill-defined, pruritic, erythematous patch or plaque, localized to the point of administration, generally transient and does not require treatment.

A number of variants have been described. Cutaneous necrosis occurs in less than 4% (12) of individuals receiving interferon-beta and appears to be less frequent with interferon-alpha (13). Management of these lesions typically involves alternating the site of injection and local wound care measures. The lesions typically resolve in one to two months.

Other injection site reactions have been reported as bullous eruptions (14), granulomatous reactions (15), injection site alopecia (16), lupus-like eruptions (17) and embolia cutis medicamentosa (18).

#### Psoriasis

Psoriasis (Figure 1) is one of the early cutaneous eruptions recognized with interferon treatment, and was reviewed as early as 1986 by Quesada and Gutterman (19). These cases are not limited to hepatitis C patients, and have been described in individuals with hepatitis B (20) and chronic myeloid leukemia (21). Since the introduction of combination ribavirin and interferon treatment, there have been four case reports of psoriasis (22-25).

The available treatment options for psoriasis in hepatitis patients are limited because common treatments such as



Figure 1) *Psoriasis*

methotrexate and cyclosporine are contraindicated due to hepatotoxicity. Clobetasol dipropionate 0.05% ointment or cream has been suggested as a cost-effective choice in Canada. Calcipotriol avoids the potential side effect of corticosteroid atrophy. Calcipotriol may be compounded with clobetasol for additional effect or used as a separate cream or ointment. Additionally, topical anthralin may be used, but it is suggested that anthralin is probably best used with ultraviolet phototherapy in a specialized psoriasis daycare facility because of the potential for staining.

#### 'Eczematoid' drug reaction

The most commonly reported nonlocal adverse effect is an eczematoid drug reaction, which has been estimated to include 59% of all noninjection site cutaneous eruptions (8) (Figure 2). Eczematoid drug reactions present as ill-defined clusters of coalescing, erythematous, blanchable, pruritic papules most commonly found on the extremities and trunk. In one early report (26), treatment was discontinued in one-half of the patients with eczematoid eruptions due to severe pruritus. However, Vazquez-Lopez et al (8) found that management with oral hydroxyzine, midpotency topical steroids and emollients allowed for uninterrupted treatment in 14 of 16 affected patients. In the remaining two patients, treatment was discontinued temporarily, then reintroduced with the addition of psychiatric treatment and support.

In most cases, the eruption can be managed without discontinuation or dose reduction of the interferon/ribavirin combination. Topical corticosteroids have been used for decades in hundreds of thousands of patients with systemic viral infections



Figure 2) *Eczema*

such as viral hepatitis and HIV, and there has been no convincing evidence that topical corticosteroids alter the natural history or response to treatment of these infections. Regardless of whether these viral infections are being treated with anti-retroviral therapy, their presence is not a contraindication to topical corticosteroids. A cost-effective therapy frequently used in Canada for this type of reaction is 0.1% betamethasone valerate cream twice daily (avoiding use on the face), with monitoring for the potential side effects of striae and cutaneous atrophy, which are particularly likely to occur within body folds.

If further symptomatic relief from pruritus is desired, this can often be addressed successfully with sedating antihistamines or antipruritic lotions and creams. If pruritus is interfering with sleep, a sedating antihistamine such as diphenhydramine or hydroxyzine at standard doses as tolerated is appropriate. Nonsedating antihistamines are generally of no benefit for the pruritus of eczematoid reactions because they do not cross the blood-brain barrier and, therefore, do not alter the sensation of itch. If pruritus predominates during the daytime, a variety of preformulated lotions and creams containing menthol and camphor, with or without pramoxine, provide immediate but short-term relief without the potential local side effects of higher-potency topical corticosteroids. The application of ice or ice-cold water also provides relief from a localized paroxysm of pruritus. Unlike topical corticosteroids, symptomatic treatment with antihistamines or antipruritics will not alter the appearance or course of the eruption.

In most cases, topical therapies and antihistamines are sufficient to allow the patient to continue therapy with interferon and ribavirin without a dose reduction. If these therapies are maximized, but not sufficiently effective, ultraviolet B phototherapy can be added, which results in a marked reduction of cutaneous inflammation without the use of a systemic immunosuppressant. It can be accessed through dermatologists' offices and hospital physiotherapy departments, but has the inconvenience of twice- or three times-weekly clinic visits. Considering that eczematoid reactions often require repeated or continuous therapy throughout the course of interferon/ribavirin therapy, every effort should be made to avoid systemic immunosuppressants such as prednisone, not

only because of the immunosuppression but also because of other long-term side effects.

### Other eczematous drug reactions

Meyerson's phenomenon, an eczematous eruption centred around pre-existing melanocytic nevi, was reported in five patients, all of whom had hepatitis C treated with combination therapy (27,28). Conde-Taboada et al (27) hypothesized that the upregulation of intracellular adhesion molecule (ICAM)-1 is responsible for the eruption. ICAM-1 is stimulated by some interferons and Meyerson's nevi have shown upregulation of ICAM-1 on keratinocytes and dermal endothelial cell surfaces.

Nummular dermatitis, a disorder of intensely pruritic, coin-shaped eczematous plaques, was observed in two patients, both of whom were being treated with combination therapy (29,30).

### Alopecia

Hair loss is a frequent adverse effect of interferon treatment and has been reported in 19% of patients treated with combination interferon and ribavirin (31). These cases typically involve a diffuse thinning of the hair.

Alopecia areata, an autoimmune condition of patchy hair loss, has been described in one patient treated with combination interferon/ribavirin for hepatitis C (32), and in a patient being treated with interferon-alpha for melanoma (33). Alopecia universalis is the most severe variant of alopecia areata in which all scalp and body hair is lost. To date, there have been four case reports of this condition, all of which were in patients who received combination treatment for hepatitis C (34-36). In three of the four cases, the alopecia universalis was reversible on cessation of the interferon treatment.

### Other hair changes

In 1999, Kadayifcilar et al (37) followed 36 patients who were treated with interferon for ocular adverse effects and found trichomegaly of the eyelashes in two patients. Since then, eyebrow and eyelash trichomegaly has been reported in five additional cases (38-42). In one of these cases, the patient was also diagnosed with porphyria cutanea tarda; therefore, the trichomegaly may have been secondary to this condition.

There are single case reports of generalized hypertrichosis (43), hair curling (44) and hair repigmentation associated with interferon treatment (45).

### Sarcoidosis

In 2005, Ramos-Casals et al (46) reported 12 new cases of sarcoidosis associated with hepatitis C infection, and also found 56 case reports in the literature. Of these 68 cases, 38 presented with predominantly pulmonary disease and 30 with predominantly skin disease. In 50 of these patients, the sarcoidosis was first identified after the initiation of treatment for hepatitis C. In 20 of 50 cases, patients were treated with interferon-alpha alone. The remaining 30 patients were treated with ribavirin and interferon-alpha combination therapy. In the majority of cases (33 of 50), sarcoidosis was detected within the first six months after the initiation of therapy. Of the above cases, only 21 required treatment. Treatment of most of these cases was with oral corticosteroids. Infliximab was reported to successfully treat interferon-related sarcoidosis in a single case (47). Remission or improvement of sarcoidosis with treatment was

described in 38 of the 46 cases in which outcome data were available. Since 2005, there have been numerous additional case reports of sarcoidosis associated with interferon treatment.

Sarcoidosis is not limited to individuals with hepatitis C because it has also been described in melanoma patients treated with interferon-alpha (48,49). Multiple case reports describe sarcoidosis first presenting within a tattoo (50-52). Therefore, the clinician must be attuned to granulomatous changes within a tattoo in patients on interferon treatment. Another clinical presentation has been involvement limited to pre-existing scars (53). A sarcoidosis-like reaction within the lacrimal gland causing orbital swelling has been reported (54,55).

### Lupus

Lupus erythematosus has been reported in four patients treated for hepatitis C (56-59), and also during treatment for multiple sclerosis (60). Lupus panniculitis has also been described in a case of multiple sclerosis (61). Arrue et al (17) found five cases of injection site reactions histologically mimicking lupus in individuals with melanoma and multiple sclerosis. Biopsy specimens demonstrated dermal mucin deposits, dense lymphocytic infiltrates along hair follicles with hydropic degeneration of the follicular basal layer, as seen in lupus. It is therefore reasonable to expect that a number of additional cases that have been diagnosed as simple injection site reactions, would likely demonstrate histological features of this localized lupus-like reaction induced by interferon. The connection between interferon and lupus is perhaps not surprising given that interferon-induced chemokines have been found to be elevated in patients with systemic lupus erythematosus (62). Therefore, exogenous administration of interferon would theoretically stimulate the same enzymes that would cause systemic lupus erythematosus in individuals who would otherwise be unaffected clinically.

### Fixed drug eruption

There have been two reported cases of interferon-associated fixed drug eruptions. One case was in a patient who was treated with combination therapy for hepatitis C (63). The patient, a 54-year-old man, developed erythematous plaques at the injection sites but also on his forehead and legs. His presentation was initially mistaken for tinea corporis. The other case was a 32-year-old woman being treated with interferon 1-beta for multiple sclerosis (64). In both cases, the lesions resolved on discontinuation of interferon therapy.

### Pigmentation disorders

Simultaneous hyperpigmentation of the tongue and the skin has been reported in three cases (65,66), all of which were in patients with hepatitis C receiving combination interferon and ribavirin therapy. Two additional cases of tongue hyperpigmentation without associated skin changes have also been reported (67,68).

Vitiligo, a disorder of patchy skin depigmentation, has been reported in a number of patients who were treated for hepatitis C with combination therapy (25,69). In one case, the vitiligo was segmentally distributed (44).

### Lichenoid eruptions

Various lichenoid eruptions have been described secondary to interferon treatment, all in the setting of hepatitis C. The prototype of these conditions is lichen planus, and this appears

to be the most commonly reported lichenoid eruption. There have been four case reports of patients on combination therapy, two of which showed predominantly oral involvement (70-74). In one case, the eruption was severe and involved the buccal mucosa, vermilion, scrotum and glans penis. The cutaneous component was successfully treated with prednisone 25 mg daily. The mucosal lesions did not respond, but required tacrolimus 0.03% solution three times daily to completely resolve. There are also single case reports of linear lichen planus (75), lichen aureus (76) and lichen nitidus (77).

#### Uncommon cutaneous reactions

There is a single study reporting three cases of aphthous ulcers (78). All of these cases involved patients being treated with combination therapy for hepatitis C.

There is a single case report (79) of Grover's disease in a patient being treated with interferon and ribavirin. Only ribavirin was discontinued and the lesions resolved, which then recurred on rechallenge. The patient was treated with a 10-day course of 40 mg oral prednisolone, and the lesions completely resolved.

There is a single case report (80) of dermatitis herpetiformis (DH) unmasked by interferon. DH is an autoimmune blistering disorder that is associated with gluten-sensitive enteropathy. DH was seen in a 52-year-old woman on combination therapy for hepatitis C. The case was associated with villous atrophy of the duodenum. Although this is an isolated case, there are other reports of gluten-sensitive enteropathy being unmasked by interferon initiation (81).

A case of delusions of parasitosis occurred secondary to interferon in a 49-year-old woman who was treated with combination therapy for hepatitis C (82). Her delusions resolved after discontinuing therapy and recurred on rechallenge.

There is a single case report of pyoderma gangrenosum secondary to interferon treatment (83). Single cases have also

been reported for granuloma annulare (84), facial erythema (85), livedo reticularis (86), 'oil cysts' (87), polyarteritis nodosa (88), systemic sclerosis (89), acral sclerosis (90), erythema elevatum diutinum (91), atrophie blanche (92), dermatomyositis (93), scleromyxedema (94), cutaneous mucinosis (95) and immune thrombocytopenic purpura (96).

Leukocytoclastic vasculitis has been reported in three cases (97-99), although this can be observed with hepatitis C alone; therefore, the cause may be difficult to distinguish.

Rosacea fulminans is a severe form of rosacea with the development of nodules and abscesses; this has been reported in two cases (100,101).

#### SUMMARY

The range of skin reactions caused by interferon and ribavirin is quite distinct from those of most other medications. Exceptions are fixed drug eruption and lichenoid eruptions that occur with interferon, ribavirin and many other drugs. Interferon has the unusual but not unexpected property of inducing reactions that resemble nondrug-induced skin diseases. This may be due to an unmasking of a predisposition to diseases such as psoriasis, eczema, lupus, sarcoidosis and alopecia areata because of pro-inflammatory properties.

SJS, TEN and systemic hypersensitivity reactions with cutaneous manifestations have not been reported with interferon alone or with the combination of interferon and ribavirin. Therefore, it is unlikely that interferon and ribavirin would have to be discontinued because of a skin side effect. Rather, the prescribing physician will likely need to be aware of techniques to recognize and manage the specific cutaneous side effects of interferon and ribavirin

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