Erythema annulare centrifugum-like eruption associated with pegylated interferon treatment for hepatitis C

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Abstract

Current standard of treatment for chronic hepatitis C virus infection requires the use of pegylated interferon plus ribavirin. Treatment with these two agents has been associated with numerous side effects, which frequently include dermatologic eruptions. We report a cutaneous eruption associated with interferon having clinical presentation of erythema annulare centrifugum. The eruption occurred within days of the first interferon injection and repeatedly flared following subsequent injections. Our patient was able to continue therapy without interruption, while managing the reaction with topical corticosteroid and oral antihistamine. We conclude that this is a benign cutaneous eruption associated with interferon which can be managed without discontinuing treatment for hepatitis C.

Case Report

A 48-year-old male was referred to our clinic for assessment of hepatitis C (HCV). His past medical history included mild chronic obstructive pulmonary disease, spinal surgery, remote eczema, and past alcohol, cigarette and intravenous drug use. He reported an allergy to penicillin and was taking naproxen daily for back pain. Treatment for HCV, genotype 1, was initiated with pegylated interferon alfa-2a 180 mcg subcutaneously once per week and oral ribavirin 1000 mg per day. On the fourth day of treatment he experienced an intermittently pruritic and enlarging rash localized to his arms and legs. He described these painless lesions as migrating cloud-like rings, which eventually became confluent with nearby lesions. Dermatologic exam one week after starting therapy showed multiple large annular erythematous lesions, each with a non-scaly peripheral red border (Figure 1). The patient denied any fevers or chills, the eruption was not localized to the injection site, there was no presence of bullae, erosions, or mucous membrane involvement. Punch biopsy was obtained; however, due to the absence of alarming symptoms we elected to continue treatment at the same dosages and manage the reaction with betamethasone valerate 0.1% cream applied twice daily along with oral hydroxyzine 25 mg as needed for pruritus.

Histopathology of the skin biopsy (Figure 2) revealed a sparse superficial perivascular infiltrate of lymphocytes and eosinophils. The epidermis was unremarkable, there was no evidence of vasculitis, and the periodic acid-Schiff (PAS) stain was negative for fungi. As well, labs at this time did not show any eosinophilia. Following the second interferon injection, the eruption flared at the same sites and had the same migratory nature as observed the prior week. The rash again improved over the next several days with topical steroids while continuing on ribavirin, yet re-emerged following the third interferon injection. The rash then completely resolved by the fourth week of interferon with no further dermatologic reactions. Diagnosis based on clinicopathology was an annular erythematous drug reaction, however the patient successfully completed 48 weeks of uninterrupted therapy and achieved cure of his hepatitis C. As well, investigations for internal malignancy have thus far been negative.

Discussion

Various cutaneous conditions have been associated with HCV infection and its treatment (Table 1).[1,2] Interferon and ribavirin therapy have been reported to cause dermatologic reactions in approximately 13-23% of HCV patients.[2] However annular erythematous eruptions associated with interferon appear rare as only one case of granuloma annulare and two cases of erythema gyratum repens have been reported in literature.[3,4] The administration of exogenous interferon alfa is thought to up-regulate hundreds of genes involved in inflammatory cell responses, along with having immunomodulating effects.[5] Therefore a cutaneous eruption following initiation of interferon is consistent with its pro-inflammatory properties.

The term erythema annulare centrifugum (EAC) was first introduced by Darier in 1916 to describe an eruption of annular lesions that enlarged rapidly then disappeared in 1 to 2 weeks while new lesions continued to develop.[6] EAC lesions usually present as erythematous macules or urticarial papules, which enlarge centrifugally and clear centrally, thereby creating an annular appearance.[7] As the edges of lesions advance, they may become confluent with adjacent lesions developing arciform segments.[7] Darier described the classical histopathologic feature as a dense perivascular *sleeve-like* lymphocytic infiltrate throughout the thickness of the dermis.[6] However since that time, the term EAC has grown to include similar presentations which have an entirely superficial histology lacking the classic *sleeve-like* arrangement.[6] Lesions of superficial EAC, unlike the deep-type, often include scaling along with nonspecific histologic findings of mild spongiosis and parakeratosis.[6] The etiology of EAC is not known, however it has been associated with a variety of etiologic factors including neoplasms, infectious agents, and several different medications.[6] Given the myriad of histologic findings and association to a variety of etiologic agents, EAC likely represents a clinical reaction pattern whose diagnosis cannot be made on pathology alone.

Our patient experienced a new migratory annular dermatologic eruption within four days of starting pegylated interferon, which was clinically indistinguishable from EAC. The lesions initially waned over the next few days while he continued taking twice daily ribavirin; however, again flared following each of the next two weekly doses of interferon. Based on the clinical presentation of his migrating lesions following interferon, distribution limited to his extremities, lack of scaling or eosinophilia, non-specific histopathology, and the resolution of symptoms without any target-

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Key words: interferon, ribavirin, hepatitis C, erythema annulare centrifugum, drug eruption.

Contributions: the authors contributed equally.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 11 June 2013.
Revision received: 5 July 2013.
Accepted for publication: 8 July 2013.

Dermatology Reports 2013; 5:e1
doi:10.4081/dr.2013.e1

Table 1. Dermatologic manifestations of hepatitis C virus and cutaneous reactions to interferon and ribavirin.

Dermatologic manifestations of HCV	Cutaneous reactions to interferon and ribavirin
Pruritus, vasculitis, urticaria, lichen planus, cryoglubulinemia, porphyria cutanea tarda, pityriasis rubra pilaris, graft-versus-host disease, polyarteritis nodosa, erythema nodosum, erythema multiforme, pyoderma gangrenosum, granuloma annulare, perniosis-like lesions, lichenoid, follicular-based purpura	Injection-site reactions, pruritus, psoriasis, alopecia, sarcoidosis, eczematoid, lichenoid, lupus, fixed-drug eruptions, pigmentation disorders, skin necrosis, Meyerson nevi

HCV, hepatitis C virus

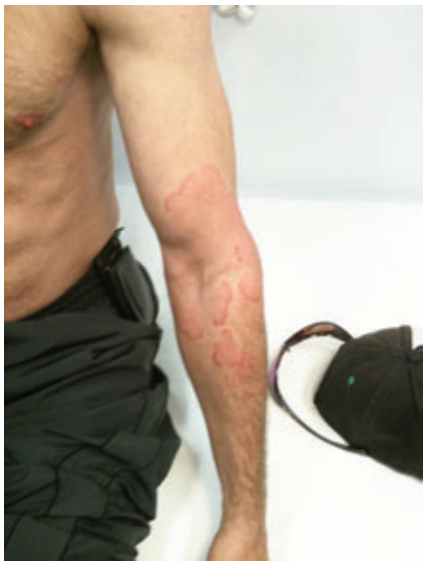

Figure 1. Patient presenting with erythematous, annular, maculo-papular lesions.

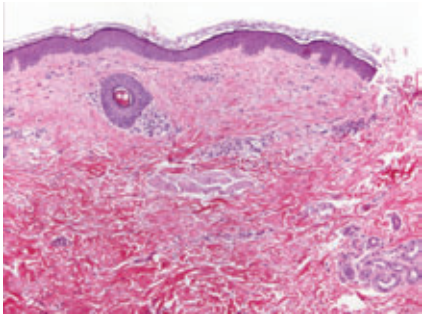

Figure 2. Histopathology showing a dermal infiltrate in superficial dermis; at 50× magnification.

ed therapy; other causes of annular lesions or migrating erythemas were excluded.[7] A primary differential diagnosis of this eruption includes a similar reactive erythema, erythema gyratum repens (EGR), which has been previously reported in association with interferon.[4] Histopathologically both EGR and superficial EAC have nonspecific perivascular lymphocytic or eosinophilic infiltrates as shown in our case. Clinically however, EGR is characterized by its *wood-grain* appearance, presents with multiple or a generalized pattern of lesions, and is associated with intense pruritus and scaling which was absent,[8] making EAC the most likely diagnosis. Therefore, we propose that interferon caused an EAC-like eruption in our patient given the clinical presentation. Although, the classical *sleeve-like* finding of deep-EAC was absent, the lymphocytic infiltrate involving eosinophils was consistent with a drug etiology.

It is unclear why despite continued treatment with interferon, the lesions did not return after resolution. Interferon is noted to promote memory T-cell proliferation, stimulate natural-killer-cell activation and dendritic-cell maturation,[5] thus it is possible the EAC-like eruption represents an up-regulated immune response to an unknown skin pathogen in our case. As well, it is possible that the etiologic agent or stimulus that induced EAC may have been eliminated. Given that the etiology of EAC has not been fully elucidated, it is difficult to speculate why continued interferon therapy did not incite more lesions, however the observations highlight that development of EAC is not a contraindication to continuing interferon treatment. Noteworthy to the clinician is that psoriatic, eczematoid and lichenoid eruptions associated with interferon therapy can also be successfully managed using corticosteroids without discontinuation of interferon.[2] As well, some reactive annular erythemas are associated with an underlying malignancy,[9] however all screening tests in our patient have remained negative. Using the Naranjo probability scale to evaluate a potential adverse drug reaction,[10] our proposed causal relationship of interferon producing this dermatologic eruption was calculated as probable.

Conclusions

Annular erythematous drug eruptions associated with interferon appear to be rare, however this report adds to the literature on this subject. In this case, recognizing the benign nature of the reaction and continuing with HCV therapy were factors enabling the patient to complete treatment and achieve cure of his hepatitis C. We conclude that in the treatment of HCV, clinicians need to distinguish benign from life-threatening dermatologic conditions in order to avoid unnecessary treatment interruption risking therapeutic failure.

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