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Low prevalence of necrolytic acral erythema in patients with chronic hepatitis C virus infection

Brian A Raphael¹, Zachariah L Dorey-Stein², Jason Lott¹, Valerianna Amorosa², Vincent Lo Re III², and Carrie Kovarik^{1,2}

¹Department of Dermatology, University of Pennsylvania, School of Medicine, Philadelphia, PA

²Division of Infectious Diseases, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

Abstract

Background—Chronic hepatitis C virus (HCV) infection is associated with necrolytic acral erythema (NAE). However, the prevalence of NAE among HCV patients is unknown, and the clinical and histological features have not been well defined.

Objective—To determine the prevalence, overall clinical features, and cutaneous histopathological characteristics of NAE patients.

Methods—A cross-sectional study was performed among chronic HCV-infected patients cared for at three Philadelphia hospitals. Patients completed a questionnaire and underwent a dermatologic examination. All undiagnosed skin lesions with clinical features of NAE as described in the literature underwent skin biopsy.

Results—Among 300 patients with chronic HCV infection (median age, 55 years; 73% male; 70% HCV genotype 1), five (prevalence, 1.7%; 95% CI, 0.5 – 3.8%) had skin lesions consistent with NAE clinically, which were analyzed and confirmed with skin biopsy. All five skin biopsies demonstrated variable psoriasiform hyperplasia, mild papillomatosis, parakeratosis, and necrotic keratinocytes in the superficial epidermis. All 5 patients were >40 years old, African American males, infected with HCV genotype 1 and had a high viral load (>200,000 IU/mL).

Limitations—Previous descriptions of NAE were used to guide the evaluation and need for a biopsy; however, other unknown clinical characteristics of the disease may exist. The senior author was the sole interpreter of the biopsies. Only 300 of the 2500 eligible patients enrolled in the study.

Conclusion—The prevalence of NAE among chronic HCV patients in this sample was very low. Further research is needed to determine the etiology and appropriate therapies of NAE.

Keywords

Necrolytic Acral Erythema; Hepatitis C; treatment; prevalence; cutaneous disease; liver disease; hepatitis C genotype

INTRODUCTION

Approximately 4 million Americans have been infected with HCV (prevalence, 1.6%), and 3.2 million are estimated to have chronic HCV infection, making this the most common blood-borne infection nationally.¹ Further, the World Health Organization estimates that 3% of the world's population is HCV-infected, with 170 million chronic carriers at risk for complications from chronic liver disease.²

While chronic HCV infection primarily affects the liver, contributing to hepatic inflammation, liver fibrosis, cirrhosis, hepatic decomposition, and hepatocellular carcinoma, it has also been associated with a number of extra-hepatic manifestations, particularly skin disease. Chronic HCV infection is associated with an increased risk of the development of cryoglobulinemia, lichen planus, porphyria cutanea tarda, polyarteritis nodosa, and generalized pruritus.³ These cutaneous diseases, while not exclusive to this patient population, occur more frequently in patients with chronic HCV.^{4–5} In addition, necrolytic acral erythema (NAE) has recently been described as a distinctive skin lesion found in patients with chronic HCV infection.^{6–7}

NAE was first described in 1996 with a series involving seven patients from Egypt infected with HCV.⁸ In subsequent years, fewer than 100 cases have been reported worldwide. The majority of patients diagnosed with NAE are from Egypt, where the overall prevalence of HCV infection is among the highest in the world at 15–20%.⁸ However, NAE has also been observed in patients with chronic HCV in the United States.^{9–10} As reported by Tabibian et al¹¹, these case reports include patients with a mean age of 40 years old and describe characteristic lesions occurring on the dorsal feet, with occasional involvement of other sites, including the legs, knees, hands, and elbows.^{8–16} Cutaneous lesions often cause burning, pain or itching and can be defined as acute or chronic.^{9, 14–15} Acute lesions are described as erythematous papules, blisters, or dusky erosions that develop in a characteristic distribution. Chronic lesions present as sharply defined hyperkeratotic plaques with surrounding erythema or hyperpigmentation and occasional crusting.^{14–16} In the past, histological findings on skin biopsy have shown a psoriasiform pattern, with varying degrees of epidermal thickness, papillomatosis, and superficial keratinocytic necrosis, depending on the chronicity of the biopsied lesion.¹⁵

Although case reports have provided a clinical description of NAE, the prevalence and risk factors for development of this disease remain unknown.^{8–16} Further, the impact of available treatments has been poorly described. We therefore sought to determine the prevalence of NAE among patients with chronic HCV infection, examine risk factors for this condition, and describe the clinical characteristics and confirm the histological features. Since NAE is a newly recognized entity described among patients with chronic HCV, delineation of its clinical features and risk factors may facilitate the initial diagnosis of this condition, provide information on its mechanism, and prompt the diagnosis and treatment of chronic HCV infection.

METHODS

Study design and setting

We performed a prospective cohort study among HCV infected subjects cared for at the Hospital of the University of Pennsylvania (HUP), Penn Presbyterian Medical Center (PPMC), and the Philadelphia Veterans Affairs Medical Center (PVAMC), all in Philadelphia, PA. These hospitals care for approximately 2,500 HCV-infected patients. The study was approved by the Institutional Review Boards of the University of Pennsylvania and the Veterans Affairs Medical Center.

Study Subjects

HCV infected patients were eligible for inclusion if they: 1) had detectable HCV RNA levels, and 2) were examined by a physician in the viral hepatitis clinics at HUP, PPMC, or PVAMC between May 2008 to February 2011. Potentially eligible subjects were identified by results of HCV viral load results generated from computer records at HUP, PPMC, or PVAMC. All eligible HCV patients were recruited for the study.

Main Outcome Measures

The primary outcome was skin lesions suggestive of NAE, defined as undiagnosed acute skin lesions (i.e., erythematous papules, blisters, or dusky erosions) or chronic skin lesions (sharply defined hyperkeratotic plaques with surrounding erythema or hyperpigmentation and occasional crusting) occurring on the dorsal feet, legs, knees, hands, or elbows.

Data Collection

All patients included in the study provided informed consent and data were collected from four sources: 1) structured questionnaire, 2) cutaneous examination, 3) medical records, and 4) biopsies of skin lesions for patients with skin findings suggestive of NAE.

At the study visit, patients completed a questionnaire administered by the study team that requested demographic information, hepatitis C treatment history, past medical problems including diabetes and chronic kidney disease, and medications actively taken. All subjects included in this study underwent a dermatologic examination by senior author (CK), who is board certified in dermatology and dermatopathology, to evaluate for the presence of skin lesions.

Following completion of the questionnaire and examination, each patient's medical records were reviewed to determine date of HCV diagnosis, medication list, and human immunodeficiency virus (HIV) infection. Laboratory data were collected, including HCV genotype, viral load, and levels of ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, INR, BUN, creatinine, glucose level, liver biopsy results and CD4 count for those infected with HIV.

Patients with undiagnosed lesions observed during physical examination underwent biopsies of skin lesions. All biopsies were punch biopsies stained with hematoxylin-eosin (H&E) and periodic acid-Schiff (PAS). The punch biopsies were conducted and analyzed by the senior author.

Data Analysis

Cohort characteristics were described using proportions for categorical data and medians with interquartile ranges (IQRs) for continuous variables. The prevalence of NAE was reported as a point estimate with a 95% confidence interval. Differences between subjects by NAE status were assessed using Chi-square or Fisher's exact tests for categorical data and Wilcoxon rank-sum tests for continuous data. All data were analyzed using Stata 10.1 (StataCorp, College Station, TX).

RESULTS

Study Cohort

Among the patients with chronic HCV infection seen at the three clinics, 300 patients participated. All the HCV positive patients seen at these three sites were eligible for inclusion into this study. The only patients that were not included into this study were those who refused to participate. The patients that did not participate did not sign a consent form

and therefore, we were unable to gather any information regarding this population. The characteristics of the participants are shown in Table 1.

Prevalence and Clinical Characteristics of Necrolytic Acral Erythema

Among the 300 chronic HCV patients, none were diagnosed with NAE prior to the study. Five patients had undiagnosed skin lesions occurring on the dorsal feet, legs, knees, hands, and/or elbows at time of presentation that were clinically suggestive of NAE (prevalence, 1.7%; 95% CI, 0.5–3.8%). The characteristics of these patients are presented in Table 2. All five patients had a previous diagnosis of HCV. These patients were all African American males. On physical examination, all five presented with hyperpigmented, well-defined, scaly plaques on the dorsal aspect of their hands and feet bilaterally. The lower legs of three of the patients were also affected, with one of the patients having significant lichenified and hyperpigmented plaques extending to the knee (Figure 1). One patient experienced minimal dryness and fissuring of the palms and soles of the feet. Plaques also presented on the trunk of one patient and elbows of another.

Histological Characteristics of Necrolytic Acral Erythema

Histologic sections of skin biopsies from lesions of 2 out of the five patients with NAE are shown in Figure 2. The histology is described in Table 2 for each patient and demonstrates papillomatosis and necrosis of keratinocytes within the very superficial epidermis. All five biopsies also showed vascular ectasia within the dermal papillae and a patchy lymphocytic infiltrate. Parakeratosis was also seen; however, it was confluent in two samples while the others showed focal distribution. All stains were PAS negative.

Treatments and Outcomes

Patient 1 received clobetasol in combination with hand and foot Psoralen with ultraviolet light A therapy (PUVA). While on therapy the lesions improved, but did not completely resolve. The PUVA was discontinued after the patient was unable to tolerate it for an extended period of time.

Patient 2 showed some improvement with topical triamcinolone, but passed away four months after NAE diagnosis from hepatic carcinoma.

Patient 3 completely cleared all cutaneous lesions after receiving a liver transplant.

Patient 4 showed modest improvement after administering narrow-band ultraviolet light B (NBUVB) therapy.

After receiving NBUVB, patient 5 experienced complete resolution of all lesions. However, he has since relapsed and uses topical triamcinolone to maintain remission. He has also initiated HCV antiviral therapy with pegylated interferon and ribavirin after being diagnosed with hepatocellular carcinoma.

None of these patients were treated with zinc for their lesions.

Discussion

In this study, we found a low (1.7%) prevalence of NAE among a cohort of chronic HCV-infected patients in Philadelphia. All of the patients diagnosed with NAE were African-American males above the age of 40. Our NAE positive patients' race is consistent with previous reports which state 92% of patients are African in origin; however, all of our patients are above the reported mean age of 40 years old described in the same review of the literature.¹¹ Our patients presented with well-defined, hyperpigmented plaques on the dorsal

aspect of their hands and feet. Tissue biopsies in those with a clinical presentation of NAE confirmed histology of NAE, as described in previous case reports, with papillomatosis, necrosis of keratinocytes within the very superficial epidermis, and vascular ectasia within the dermal papillae and a patchy lymphocytic infiltrate.

The 1.7% prevalence we found in this study was lower than expected. The lower than expected prevalence is possibly due to the difference of HCV genotypes seen here in the United States compared to Egypt. Therefore, it is possible that the genotype plays a critical role in the manifestation of this cutaneous disease.

Our report indicates that NAE primarily affects the dorsal aspects of the patients' hands and feet bilaterally. However, we also observed that lesions extended to the legs and trunk. NAE lesions have been characterized as well-defined erythematous to violaceous hyperpigmented plaques with scale. The histologic presentation of NAE demonstrates papillomatosis and necrosis of keratinocytes within the very superficial epidermis, as well as vascular ectasia and lymphocytic infiltrate in the dermal papillae. Although NAE is difficult to diagnose and has been mistaken for other cutaneous diseases such as psoriasis or pellagra, the combination of these clinical appearances with the histology described in our patients should be used to diagnose NAE. Clinically applying this information can help correctly diagnose future NAE cases.

Due to the low prevalence we were unable to perform a sound analysis to determine risk factors for NAE. However, since our cohort included a large number of patients co-infected with HIV who did not show any signs of NAE, it is unlikely that NAE is caused by immunodeficiency or co-infection. Many of our patients who did not have NAE were reported to have high HCV viral loads, and we therefore think that HCV viral load is also unlikely to be the direct cause of NAE. Although we did not analyze zinc levels, if this were the etiology of the disease, it would not account for three of our patients' NAE resolving following PUVA or steroids therapy. Due to our patient's NAE resolving with different treatments, we suggest that the etiology is multifactorial with the pathogenesis of the disease stemming from the liver dysfunction. Nutritional deficiency and other previously suggested causes may only be confounding factors.

Since Patient 3's NAE resolved following a successful liver transplant it is possible that this disease might manifest as a result from liver dysfunction. However, we are unable to determine whether the virus has a direct effect or establishes a unique milieu that propagates NAE. It is possible that the virus creates a specific environment for NAE to present which can explain why NAE is not seen in other liver diseases. Although HCV causes elevated liver function lab values, patients diagnosed with NAE had higher levels of bilirubin, AST and ALT than those in the control cohort. Only two patients diagnosed with NAE received liver biopsies. More research is needed to determine whether liver dysfunction, evaluating complete measures of liver function and histology of the liver, rather than previously purposed etiologies such as zinc deficiency or depressed immune system from co-infection, may be the general underlying cause of this cutaneous disease.

There were some limitations to this study. Although few patients refused to participate in this study, all were eligible for inclusion, limiting any selection bias. This study used clinical presentations of NAE described in the literature to guide the evaluation and need for a biopsy; however, there may be other clinical characteristics of the disease that have not yet been described. In addition, it is possible that existing skin lesions may have been clinically misdiagnosed and not biopsied. The senior author was the sole interpreter of the punch biopsies leading to possible interpretation bias.

In summary, it is important to establish the diagnosis of NAE in order to detect the HCV infection status as early as possible. The etiology for NAE remains unknown; however, we suggest that it is multifactorial with liver dysfunction caused by HCV as a main proponent for the appearance of NAE. Therefore, more research is necessary, specifically focusing on liver function such as biopsies and lab values to determine an association with NAE.

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Figure 1. Necrolytic Acral Erythema. Well defined dusky, hyperkerototic plaques on the shin and dorsal foot of a patient with necrolytic acral erythema (NAE).

Figure 2. Necrolytic Acral Erythema. Histopathology of punch biopsy from a hyperkeratotic plaque showing papillomatosis, necrosis of keratinocytes within the very superficial epidermis, vascular ectasia within the dermal papillae, and a patchy lymphocytic infiltrate. Original magnification X100 (A) and X200 (B)

Table 1

Patient demographics and characteristics

Characteristics	All Subjects (N=300)	NAE (N = 5)
Median age (yrs, IQR)	55 (50 – 59)	55.2 (52 – 60)
Male sex (no., %)	218 (73%)	5 (100%)
Race (no., %)		
African-American	150 (50%)	5 (100%)
Caucasian	130 (43%)	0 (0%)
Hispanic (no., %)	13 (4%)	0 (0%)
HCV genotype (no., %)		
1	211 (70%)	3 (60%)
2,3	18 (6%)	0 (0%)
Missing	71 (24%)	0 (0%)
Median HCV RNA level (IU/mL, IQR)	1,235,205 (245,932 – 3,619,350)	21,271,000 (886,000 – 2,320,000)
METAVIR stage of hepatic fibrosis *	103 (34%)	2 (40%)
F0–2	39 (13%)	2 (40%)
F3–4	158 (53%)	0 (0%)
No results available		3 (60%)
METAVIR grade of liver inflammation *	46 (15%)	1 (20%)
G0–1	85 (28%)	0 (0%)
G2–3	169 (56%)	1 (20%)
No results available		4 (80%)
History of antiviral therapy for chronic HCV (no., %)	135 (45%)	2 (40%)
HIV infection (no., %)	86 (29%)	2 (40%)
Diabetes mellitus (no., %)	93 (31%)	2 (40%)
Chronic kidney disease (no., %)	19 (6%)	0 (0%)
Median total bilirubin (ng/mL, IQR)	0.7 (0.5 – 1.1)	3.82 (0.6 – 5.9)
Median ALT (U/L, IQR)	49 (31 – 81)	233.8 (63 – 135)
Median AST (U/L, IQR)	53 (35 – 88)	727.8 (97 – 108)

* Some liver biopsies report stage only with no grade

Table 2

Demographic and clinical characteristics of patients confirmed to have necrolytic acral erythema.

Patient	Age at Diagnosis	Race	Gender	Medical History	HCV Genotype	Viral Load (log IU/ml)	ALT (U/L)	AST (U/L)	Total Bilirubin (mg/dl)	International Normalized Ratio	Creatinine (mg/dl)	Histopathology Of Biopsy
1	69	African American	Male	HIV+ DM	1	986*10 ³	36	63	5.9	1.23	0.68	Psoriasiform hyperplasia with vague papillomatosis and confluent necrosis of keratinocytes within the very superficial epidermis. The papillary dermis shows mild vascular ectasia within the dermal papillae and a sparse lymphocytic infiltrate
2	60	African American	Male	--	1	886*10 ³	862	3272	8.2	2.05	1.78	Epidermal acanthosis with exaggerated papillomatosis and focal parakeratosis. Focal necrosis of keratinocytes and epidermal pallor within the very superficial epidermis. The papillary dermis shows vascular ectasia within the dermal papillae and a patchy lymphocytic infiltrate.
3	52	African American	Male	HIV+	--	102*10 ⁶	73	99	0.6	--	1.21	Irregular acanthosis with significant papillomatosis, focal spongiosis, hyperkeratosis, and parakeratosis. Focally confluent necrosis of keratinocytes within the superficial epidermis. The papillary dermis shows mild vascular ectasia within the dermal papillae and a sparse lymphocytic infiltrate.
4	40	African American	Male	--	1	232*10 ⁴	135	108	3.3	1.12	0.85	Mild epidermal acanthosis with significant papillomatosis and hyperkeratosis. Focally confluent necrosis of keratinocytes within the very superficial epidermis. The papillary dermis shows vascular ectasia within the dermal papillae and a patchy lymphocytic infiltrate with pigment incontinence
5	55	African American	Male	DM	--	223*10 ³	63	97	1.1	--	0.97	Epidermal acanthosis with exaggerated papillomatosis and focal parakeratosis. Focal necrosis of keratinocytes within the very superficial epidermis is present. The papillary dermis shows vascular ectasia within the dermal

Patient	Age at Diagnosis	Race	Gender	Medical History	HCV Genotype	Viral Load (log IU/ml)	ALT (U/L)	AST (U/L)	Total Bilirubin (mg/dl)	International Normalized Ratio	Creatinine (mg/dl)	Histopathology Of Biopsy
												papillae and a patchy lymphocytic infiltrate.

HIV – Human Immunodeficiency Virus, DM – Diabetes Mellitus, ALT – Alanine Aminotransferase (nl 21–72), AST – Aspartate Aminotransferase (nl 17–59), Total Bilirubin (nl 0.0–1.2), International Normalized Ratio (nl 0.8–1.2), Creatinine (nl 0.8–1.3)