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ORIGINAL ARTICLE

The prevalence of HCV antibodies in skin disease patients in Saudi Arabia

Mona Halawani [a,*], Amal Balbisi [a], Hend Alotaibi [a], Fahed Alsaif [a], Talal M. Bakir [b]

[a] *Department of Dermatology, King Khalid University Hospital, Riyadh, Saudi Arabia*
[b] *Department of Clinical Lab Science, College of Medical Applied Sciences, King Saud University, Riyadh, Saudi Arabia*

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Abstract *Background/aim:* Hepatitis C virus (HCV) infection is a worldwide health issue with about 3% of the world's population having HCV. In Saudi Arabia, prevalence ranges from 1.0% to 5.87%. Cutaneous diseases can indicate the presence of HCV infection.

Objectives: The research project aims to identify prospectively the prevalence of HCV infection in 200 patients with various types of skin disorders and 50 healthy blood donors, and to quantify this association through clinical and laboratory investigations.

Methods: Two hundred patients with cutaneous manifestations who presented at the Dermatology outpatient clinics of King Khalid University Hospital (KKUH) and King Abdulaziz University Hospital (KAUH), Riyadh, and 50 healthy blood donors were prospectively studied. Patients were examined by a team of dermatologists and clinical data were collected through a standard questionnaire. Ten milliliters of venous blood were collected from fully consented, 8–10 h fasting patients and serum was analyzed for AST, ALT, double infection with HBsAg, anti-HCV antibodies, and screened for HCV-RNA-PCR.

Results: Patients from the study (n = 200) consisted of 25 (12.5%) males and 175 (87.5%) females, with a mean age of 42.9 ± 15.06 years. Clinical examinations revealed that (35%) had urticaria, followed by pruritus (28%), lichen planus (25.5%), prurigo (10%), and palpable purpura (1.5%). The main serum levels of ALT and AST were within the normal reference ranges. Twenty-four patients (12%) tested positive for anti-HCV antibodies, with 15 (62.5%) being positive for the presence of HCV-RNA by PCR and 9 (37.5%) resulting negative for the viral RNA. Of the

* Corresponding author.
E-mail address: Monahalawani@gmail.com (M. Halawani).

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24 anti-HCV positive patients, pruritus 12 (50%), urticaria 5 (20.8%), lichen planus 5(20.8%), and palpable purpura 2(8.3%). Five (2.5%) patients were positive for HBsAg, with 3 (60%) having pruritus and 2 (40%) presenting with urticaria. Of the 50 healthy blood donors, only one (2%) tested positive for the presence of anti-HCV antibodies, and all the donors tested negative for HBsAg.

Conclusion: Results clearly indicate the prevalence of anti-HCV antibodies in 24 out of 200 patients (12%) with skin manifestations seen at the dermatology outpatient clinics and documented with HCV-RNA-PCR positivity of 15/24 (62.5%). A p-value of <0.05 was considered significant, therefore, it is suggested that patients presenting with urticaria, pruritus and LP be investigated to exclude the possibility of HCV infection.

1. Introduction

Many reports have shown that cutaneous manifestations are often the first signs of chronic HCV infection and these are indicated in 20–40% of the patients presenting to the dermatology clinics, therefore dermatologists must be aware of skin disorders associated with viral infection Schwartz and Birnkrant, 2008; Galossi et al., 2007. The most commonly encountered dermatological manifestations of HCV infection includes mixed cryoglo-bulinemia (MC), porphyria cutanea tarda (PCT), cutaneous and/or oral lichen planus (LP), urticaria, pruritus, thrombocytopenic purpura and cutaneous vasculitis (Schwartz and Birnkrant, 2008; Galossi et al., 2007; Poljacki et al., 2000; Cordel et al., 2000). Although majority of skin manifestations of chronic HCV infection represent the clinical impression of autoimmune phenomena, however, precise pathogenesis of these extra-hepatic complications is not well understood (Pyropoulos and Reddy, 2001; Dega et al., 1998).

The most documented extra-hepatic manifestation of HCV infection is MC, and is reported in about half of all the HCV patients (Schott et al., 2001). Chronic HCV infection has also been associated with PCT (Bulaj et al., 2000). Similarly, the presence of increased frequency of HCV among LP patients has put LP as one of the primary skin disorders associated with the chronic HCV infection (Nagao et al., 2000; Arrieta et al., 2000; Mignogna et al., 2000). Pruritus is also implicated in advanced chronic HCV infection and has been documented in 5–15% of patients, with chronic HCV infection (Dega et al., 1998). There have been conflicting reports both in favor of and against HCV-causing urticaria (Llanos et al., 1998).

This study was conducted to estimate the prevalence of HCV exposure in skin disease patients and analyze the frequency of HCV infection in patients with skin disease.

2. Methods

Demographic (age, sex, nationality, marital status) and clinical data (symptoms, sign, past-medical history and predisposing risk factors for HBV and HCV infection, types of skin disease and its duration) of skin disease patients presenting with pruritus, prurigo, urticaria and/or LP and healthy blood donors ($n = 50$) were collected through a standardized questionnaire conducted and examined by consultant dermatologists at King Khalid University Hospital (KKUH) and King Abdulaziz University Hospital (KAUH), Riyadh, Saudi Arabia. Ten milliliters of whole blood were collected from healthy blood donors and 8–10 h fasting skin disease patients, after consent. Sera were separated by centrifugation at 2500 rpm for 15 min at 4 °C, transferred in 1 mL quantities to four properly labeled containers, and stored immediately at −70 °C until the laboratory testing was performed for AST, ALT and HCV/HBV serology at KKUH laboratories.

According to the manufacturer standard proto-cols, the following laboratory tests were done. Serum ALT and AST were determined using Automated Multi-Channel Clinical Chemistry Analyzer. Anti-HCV antibodies were detected using Ortho HCV 3.0 ELISA Test System (Ortho-clinical Diagnostics, Inc., UK). Anti-HCV positive samples were confirmed by LIA (Lia Tek HCV III, Organon Teknika, Germany). Commercially available ELISA kits (Hepanostika HBsAg Uni-Form II Microelisa system; Biomerieux bv, Boseind 15, Netherlands) were used for the determination of HBsAg in patient's and healthy blood donors, and anti-HCV positive sera were analyzed using COBAS AMPLI-COR HCV ASSAY (Version 2-Roche Diagnostic Systems, Germany).

Results of 200 skin disease patients and 50 healthy blood donors were analyzed using Statistical Package for Social Sciences (SPSS) version 11.5 and are reported as mean ± standard deviation. Student's t-test (two-tailed) was used to examine the significance of difference between the two sets of data, and a p-value of <0.05 was considered significant.

3. Results

A total of 200 skin disease patients, consisting of 25 (12.5%) males and 175 (87.5%) females with a mean age of 42.9 ± 15.1 years (range: 8–80 years) was studied (Table 1). The highest prevalence of HCV and HBV risk factors among skin disease patients was the history of intramuscular injection (Table 2). Among the various types of skin manifestations, urticaria was the most prevalent at 35% ($n = 70$) followed by pruritus (28%), LP (25.5%) and prurigo (10%). Palpable purpura was reported in three patients (1.5%) as seen in Tables 2 and 3.

The prevalence of anti-HCV, HBsAg and HCV-RNA-PCR positivity is shown in Table 3. Among 51 patients with LP, 5 (9.8%) were anti-HCV positive, of which 2 (40%) were HCV-RNA-PCR positive, none of which turned out positive for HBsAg. Of 56 patients with pruritus, 12 (21.4%) were anti-HCV positive of which 9 (75%) were HCV-RNA-PCR positive and 3 (5.4%) were HBsAg positive. Among 70 patients with urticaria, 5 (7.1%) were anti-HCV positive of which 3 (60%) were HCV-RNA-PCR positive and 2 (2.9%) were positive for HBsAg. Of 20 patients with prurigo, two were anti-HCV and HCV-RNA-PCR positive, and none were

Table 1 Demographic data of skin disease patients and healthy controls.

	Skin Disease Patients	Healthy controls
No. of patients	200	50
Males	25 (12.5%)	44 (88%)
Females	175 (87.5%)	6 (12%)
Age in years (mean ± SD)	42.9 ± 15.1 (range: 8–80 years)	25.5 ± 7.4 (range: 18–41 years)
Anti-HCV positive	24 (12%)	1 (2%)
Anti-HBsAg positive	5 (2.5%)	0

Table 2 Prevalence of HCV and HBV risk factors among skin disease patients (n = 200).

Parameters	No. (%)	L. planus	Pruritus	Urticaria	Prurigo	Palpable purpura
Total number of patients	200	51 (25.5)	56 (28)	70 (35)	20 (10)	3 (1.5)
Jaundice	11 (5.5)	2 (3.9)	6 (10.7)	2 (2.9)	1 (5)	0
Contact with jaundiced patient	10 (5)	2 (3.9)	4 (7.2)	3 (4.3)	1 (5)	0
Blood transfusion	33 (16.5)	7 (13.7)	12 (21.4)	10 (14.3)	3 (15)	1 (33.3)
Use of blood products	2 (1)	0	1 (1.8)	1 (1.4)	0	0
History of intramuscular injection	36 (18)	7 (13.7)	9 (16.1)	15 (21.4)	2 (10)	3 (100)
History of drug abuse	0	0	0	0	0	0
Sexual contact with HCV/HBV patient	10 (5)	2 (3.9)	4 (7.2)	3 (4.3)	1 (5)	0
Contact with HCV/HBV family member	15 (7.5)	5 (9.8)	3 (5.4)	5 (7.2)	2 (10)	0

Table 3 HBV and HCV in skin disease patients.

HCV parameters	No. (%)	L. planus	Pruritus	Urticaria	Prurigo	Palpable purpura
Total number of patients	200	51 (25.5)	56 (28)	70 (35)	20 (10)	3 (1.5)
HBsAg positive	5 (2.5)	0	3 (5.4)	2 (2.9)	0	0
HCV antibody negative	171 (85.5)	46 (90.2)	41 (73.2)	63 (90)	20 (100)	1 (33.3)
HCV antibody positive	24 (12)	5 (9.8)	12 (21.4)	5 (7.1)	2 (10)[a]	2 (66.7)
HCV-RNA-PCR positive	15 (62.5)	2 (40)	9 (75)	3 (60)	2 (10)	1 (50)
HCV-RNA-PCR negative	9 (37.5)	3 (60)	3 (25)	2 (40)	0	1 (50)

[a] Patients having prurigo with L. planus and palpable purpura.

HBsAg positive. Of the 3 patients with palpable purpura, 2 (66.7%) were anti-HCV positive of which 1 (50%) were HCV-RNA-PCR positive and none were HBsAg positive (Table 3). All of the 24 anti-HCV positive skin disease patients were subjected to HCV-RNA-PCR screening employing standard protocols and molecular biology techniques. Of those 24 patients, 15 (62.5%) tested positive for the presence of viral RNA by PCR screening, whereas 9 (37.5) were HCV-RNA-PCR negative (Table 3).

The association between various types of skin manifestations and anti-HCV positive skin disease patients' AST and ALT values with the exception of LP (n = 5) and prurigo (n = 2), patients who had pruritus (n = 12), urticaria (n = 5), and palpable purpura (n = 2), had their mean serum ALT activity within the normal reference ranges (20–65 U/L). Although the number of patients were very limited, however, both LP (n = 5; 80.80 ± 8.58; 71–95 U/L) and prurigo (n = 2; 79 ± 2; 77–81 U/L) were associated with higher ALT activity as compared to pruritus (48.38 ± 22.77; 17–84 U/L; p = 0.008), urticaria (31.8 ± 16.48; 16–58 U/L; p = 0.004), and palpable purpura (53.5 ± 23.5; 30–77 U/L; p = 0.037). Unlike the ALT, the mean serum AST concentration among our anti-HCV positive skin disease patients was slightly elevated above the normal range in all the categories of patients including prurigo (65.5 ± 0.50; 65–66 U/L), LP (52.2 ± 22.23; 36–66 U/L), pruritus (46.5 ± 13.97; 24–73 U/L), and palpable purpura (42 ± 23; 19–65 U/L), except urticaria where AST was within the normal reference number range (26.67 ± 9.69; 15–40 U/L).

In addition to the 200 skin disease patients, 50 healthy blood donors were also studied as "healthy controls" for the validation of research methodology and laboratory protocols. These blood donors were recruited through blood banks at KKUH, Riyadh, and were examined by consultant dermatologists. Their demographic/clinical data and blood samples were collected and analyzed. These blood donors consisted of 44 (88%) male and 6 (12%) female with a mean age of 25.5 ± 7.4 (range: 18–41 years). The majority were Saudi (96%) and were married (76%). Their clinical examination did not reveal any skin manifestations and none of them reported past exposure to any of the HCV risk factors. One of the 50 blood donors (2%) tested positive for the presence of anti-HCV antibodies while all of the donors tested negative for HBsAg. Anti-HCV positive blood donor's sample was subjected to HCV-RNA-PCR screening which tested negative for the presence of HCV-RNA.

4. Discussion

Our results are in agreement with previous reports from Saudi Arabia as well as other countries which indicate that persistent exposure to HCV risk factors significantly predisposes healthy population to the risk of acquiring HCV infection (Bakir, 1992; Fakeeh and Zaki, 1999; Sandhu et al., 1999; Flamm et al., 1998; Karkar, 2007; Sharara et al., 1996).

HBsAg was detected in only 5/200 (2.5%) whereas none of the 200 skin disease patients tested positive for both HBV and HCV. Despite the fact that HBV was more prevalent among Saudi population than HCV, our results suggest that skin manifestations of viral hepatitis may be associated more with HCV than HBV among chronic hepatitis patients.

Of the total 200 studied patients, 24 (12%) tested positive for anti-HCV antibodies, showing a significantly higher prevalence than the existing prevalence of 0.1–6.9% among Saudi population (Bakir, 1992; Madani, 2007; El-hazmi, 2004). Fifty percent of our anti-HCV positive skin disease patients had pruritus followed by LP (20.83%) urticaria (20.83%), palpable purpura (8.3%) and prurigo (8.3%). Our results are not in total agreement with many studies from Western countries which have shown MC and PCT as the most predominant extra-hepatic skin manifestations among chronic HCV patients (Galossi et al., 2007; Sterling and Bralow, 2006). As 50% of our pruritus patients were positive for anti-HCV antibodies, therefore, it is suggested that such cases should be screened for anti-HCV antibodies as well as HBsAg. Another study showed that the most common skin disease among chronic HCV patient was generalized pruritus (18.57%), followed by LP (4.28%) Dervis and Serez, 2005. Similarly, Bonacini reported that 20% of their chronic hepatitis C patients presented with pruritus (Bonacini, 2000). Reports from France and USA have also shown that pruritus has been documented in 5.0–15% of patients with chronic HCV infection (Cordel et al., 2000; Jackson, 2002).

Several studies have shown that 15–35% of LP patients have hepatic disorders Nagao et al., 2000. We found both LP and urticaria present among anti-HCV positive skin disease patients (20.83%). This is in agreement with the study done in Saudi Arabia by Asaad and Samdani (2005) where 114 LP patients (26.3%) tested positive for anti-HCV antibodies.

Five (20.83%) of our anti-HCV positive patients had urticaria showing a weaker association with HCV as compared to pruritus (50%). Whether hepatitis C infection causes urticaria or not is still a debatable issue and there have been conflicting reports both in favor of and against HCV-causing urticaria (Llanos et al., 1998). Several studies have suggested that HCV status should be checked in patients presenting with urticaria in areas with a high HCV prevalence (Paoletti et al., 2002; Crowson et al., 2003).

Although 20 (10%) of our studied patients had prurigo, none of them tested positive for anti-HCV antibodies except two patients who already had LP and palpable purpura, respectively. According to our findings, the association between HCV and prurigo is poor, as compared to both pruritus, urticaria and LP. The relationship between chronic HCV infection and prurigo is not well documented. Podányi et al. (2004) described two chronic HCV patients with intense pruritis and secondary prurigo. In our study three patients had palpable purpura of which two tested positive for anti-HCV antibodies. Currently, there are no data available from Saudi Arabia regarding the prevalence of palpable purpura in Saudi population and its association with HCV.

Fifteen (62.5%) of our anti-HCV positive skin disease patients tested positive for the presence of viral RNA thereby reflecting an active HCV replication (viremia) among these patients. On the contrary, only one of the healthy blood donors tested positive for anti-HCV, however, it was negative for HCV-RNA by PCR. The presence of statistically significant high prevalence of HCV-RNA in our studies skin disease patients is suggestive of an etiological role of HCV infection in various types of skin manifestations.

In the present study, we could not find a significant difference in LFT markers between various categories of our studied skin disease patients.

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