Dermatological manifestations of hepatitis C virus infection in Saudi Arabia

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**ABSTRACT**

The Saudi Ministry of Health data indicates that almost 32% of viral hepatitis cases were caused by hepatitis C virus (HCV). It has been widely reported that chronic HCV infection is associated with and may trigger or exacerbate many skin manifestations in 20-40% of patients visiting dermatologists. The most commonly encountered dermatological manifestations of HCV infection globally include mixed cryoglobulinemia, porphyria cutanea tarda, cutaneous and/or oral lichen planus, urticaria, pruritus, thrombocytopenic purpura, and psoriasis. The current article indicates that HCV infection is increasing in Saudi Arabia and approximately 12% of the reported dermatological manifestations are caused by HCV infection. We recommend the urgent need for large-scale, case-control studies to understand the impact of HCV infection in patients with skin disease.

**Prevalence of HCV in the Kingdom of Saudi Arabia (KSA).** Hepatitis C virus significantly affects human health and is the most important cause of liver disease worldwide with the World Health Organization (WHO) estimating 3% of the global population to be infected with HCV. The number of individuals estimated to be infected with HCV exceeds 170 million (Figure 2); however, the prevalence of the infection varies in different geographic areas. In the Arab world, the prevalence of HCV infection varies markedly from 1.7-25% with an increasing trend in the HCV incidence. The sero-prevalence of HCV among the healthy Saudi population has been reported to range from 0.2-1.7% for adults, and 0.01-0.1% for children. Several studies conducted in Saudi
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Arabian children revealed that of the different regions, the Giza population had the highest prevalence of HCV antibodies and seroprevalence increased with age. Although an annual increase of HCV infections was observed from 1998-2002, another study in the eastern province of KSA indicates a decline in the prevalence of HCV in blood donors from 1% in 1998 to 0.59% in 2001.

The Saudi Ministry of Health data indicates that almost 32% of viral hepatitis cases were caused by HCV. Hepatitis C virus is one of the major causes of disease requiring liver transplantation and of liver cancer, resulting in enormous health care utilization expenses. Viral hepatitis surveillance data at King Abdulaziz Medical City in Riyadh for the past 8 years indicated a decreasing trend in this infection; however, there could have been an underestimation of prevalence in previous reports. A study by Al-Ajlan determined the prevalence of anti-HCV antibodies among 16570 students (9852 male, 6718 female, mean age: 21 years) at various health colleges in KSA from 2000-2007. The results showed that the prevalence of anti-HCV for males was 0.03% and females 0.07% in the 18-21 year age groups, and 0.31% (male) and 0.40% (female) in the 22-30 year age group.

Extra-hepatic manifestations of HCV infections. Chronic HCV infection is usually accompanied by systemic, non-specific or autoimmune disorders along with extra-hepatic manifestations. Up to 40-76% of patients infected with HCV might develop at least one extra-hepatic manifestation during the course of their disease. Older age, female gender, and extensive liver fibrosis were reported to be the most common risk factors associated with the presence of extra-hepatic clinical or biologic abnormalities in HCV patients. The organs and systems reportedly affected during infection with HCV are the kidneys, skin, thyroid, eyes, joints

Figure 1 - Structure of hepatitis C virus. RNA - ribonucleic acid

Figure 2 - World-wide prevalence of hepatitis C virus infection. Adapted from: http://wwwn.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/hepatitis-c
(arthralgias), and nervous system. In addition, it has been hypothesized that the extra-hepatic manifestations of HCV infection could be the initial indicators in a patient with no hepatic symptoms.

**Predominant dermatological manifestations of HCV infection in KSA.** Dermatological lesions are one of the clinical evidences of the underlying liver disease and are observed in 20-40% of the HCV patients. The clinical features of chronic HCV are typical with an autoimmune reaction; however, mechanisms involved in the development of extra-hepatic complications is not totally clear. Schwartz et al and Dega et al reported that cryoglobulinemia, porphyria cutanea tarda (PCT), oral lichen planus, urticaria, pruritus, thrombocytopenic purpura are the most common observed skin diseases associated with HCV infection. A study by Amin et al reported that the most common cutaneous manifestations of HCV infection were pruritus, lichen planus (LP), hyperpigmentation, and urticaria. A higher frequency of HCV infection compared with normal population was observed in patients with LP, pruritus, urticaria, prurigo and PCT. However, a prospective study conducted in Riyadh on 200 skin disease patients to identify the prevalence of HCV infection in subjects with skin disorders showed that 24 (12%) tested positive for anti-HCV antibodies in whom the most common skin manifestations included pruritus (50%), urticaria (20.8%), LP (20.8%), prurigo (8.3%), and palpable purpura (8.3%). In a study conducted by Abulhassan et al a high prevalence (62.5%) of cryoglobulinemia was observed in patients with chronic HCV. They presented with symptoms of fatigue (67.5%), arthralgia (32.5%), paresthesia (30%), and pruritus (25%). Other skin manifestations in these included PCT (20%), and LP (17.5%).

Urticaria is a common disorder that affects as much as 20% of the general population at some point during their lifetime. Urticaria is believed to be caused or aggravated by drugs, foods, additives, connective tissue disorders, and infections. Whether hepatitis C infection causes urticaria and the related etiopathogenic process remains unclear and warrants further investigations, although, it is thought to be related to the presence of immune complexes in persistent HCV carriers. While Llanos et al and Smith et al did not find an association between HCV and urticaria, Siddique et al and Kanazawa et al reported a positive relationship between HCV and urticaria. Several studies have suggested that HCV status should be checked in patients with urticaria in areas with a high HCV prevalence. Dega et al stated that 18% of patients with urticaria had HCV antibodies while Kanazawa et al detected anti-HCV in 24% of patients with urticaria. On the other hand, Cribier et al claimed that antibodies to HCV were found in only one patient with urticaria and one among the control group (0.9% of each group), and that HCV is unlikely to be the cause of urticaria due to the absence of HCV RNA. This finding was also seen by Llanos et al and Smith et al. Halawani et al showed that both LP and urticaria were present among anti-HCV positive patients with skin disease (20.8%), which is in agreement with the study of Asaad and Samdani, Dega et al, Kanazawa et al, and Halawani investigated the HCV genotypes in urticaria patients of KSA. Anti-HCV antibodies were found in 7.1% of urticaria patients. Genotypes 3 and 4 with subtypes 3a, 4a, and 4c were found. This study indicated that the increased sero-positivity of HCV infection among urticaria patients indicated a significant association with disease pathology. Similar positive relationships between HCV and urticaria were reported in some studies, while a few studies reported only weaker or no association between HCV infection and urticaria.

Pruritus, a common skin manifestation of advanced chronic HCV infection was found among 15% of HCV patients; similar incidence rates have been reported elsewhere. The highest prevalence reported so far was by Dega et al, where 70% of HCV patients complained of pruritus. Hepatitis C virus was found to be significantly predominant among pruritus patients. This study was conducted in patients attending 2 dermatology clinics at King Khalid University Hospital and King Abdul Aziz University Hospital, Riyadh, KSA. A significant association was found between pruritus and HCV infection, which was in agreement with other studies. Soylu et al conducted a study in patients positive for anti-HCV antibodies to analyze the frequency of cutaneous findings and showed that the risk of developing pruritus was increased during HCV infection. The precise mechanism of pruritus in liver diseases remains unclear, the presence of bile salts in the skin, histamine, and alternative liver metabolites have been proposed as explanations.

Lichen planus, a chronic inflammatory cutaneous disease characterized by itchy, flat-topped, polygonal, glistening papules that affects 0.5-2% of the general population. The American Skin Association suggests that at least a few cases of LP are associated with chronic HCV infection, and cases of erosive LP of the scalp have also been reported. The role of infection in the development of LP has been repeatedly raised over the years. Hepatitis C virus has also been implicated in triggering LP. Genetic factors controlling disease susceptibility and prevalence of certain HCV genotypes...
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in certain geographic areas may have significantly influenced the variation of prevalence of HCV with LP. A new study conducted in a Japanese population found a high prevalence of HCV in patients with oral LP, and the prevalence of anti-HCV was found 67.8%, and HCV RNA was 59.3%. In contrast, a study conducted in an Indian population by Patil et al. showed no evidence of HCV infection in patients with oral LP. The mechanism that links LP and HCV infection remains unclear, but could be due to an aberrant immunologic response. Although the etiology of HCV induced LP is unknown, it is probably related to viral replication in lymphocytes. Lazaro et al. demonstrated that HCV infects keratinocytes from cutaneous LP lesions and that the viral RNA is translated in these cells as demonstrated by the HCV incorporated in the skin biopsies. Similarly, the presence of increased frequency of HCV among LP patients has put LP as one of the skin disorders associated with chronic HCV infection. Studies recommend regular screening for LP in HCV positive patients for early diagnosis, probably because HCV seropositivity may increase the risk for LP. Asaad and Samdani observed that 26.3% of patients with LP had HCV antibodies, while only 4.6% patients from the control group were positive for HCV infection. A recent meta-analysis exploring the association between HCV and LP, revealed an important association for the prevalence of HCV infection among patients with LP compared with controls. Both LP (20.8%) and urticaria (20.8%) were present among Saudi anti-HCV positive skin disease patients.

Prurigo. Schwaber and Zlotogorski reported that at least 39% of their tested general dermatological patients had evidence of HCV infection while only 5% of those without any skin manifestation had serologic evidence of HCV disease. In a study conducted by Halawani et al in 2010, although 20 (10%) of the studied patients had prurigo, yet only 2 of them tested positive for anti-HCV antibodies and already had LP and palpable purpura, indicating a poor association between HCV and prurigo. Prurigo could be as a result of accidental disease such as HCV presenting clinically as prurigo nodulosis, which is caused by severe chronic pruritus or may have mixed causes. Podanyi et al. reported 2 patients with intense pruritus and secondary prurigo are positive for chronic HCV infection. The pathological mechanism involved in prurigo is thought to be related to immune complex in persistent HCV carriers.

Porphyria cutanea tarda (PCT). Porphyria cutanea tarda occurs as a result of defect in the heme synthesis pathway where uroporphyrinogen decarboxylase (UROD) becomes deficient or absent. The presumed pathogenesis of HCV-triggered PCT involves de-compartmentalization of iron stores resulting in liberation of free iron radicals and oxidation of UROD. The prevalence of HCV infection in PCT patients is different not only between different countries but also within different geographical locations in each country. In southern Europe where HCV is widespread, 70-90% of patients with PCT are positive for HCV infection while in northern Europe where HCV is infrequent, only 20% of patients with PCT have detectable levels of HCV. The study conducted by Halawani et al. showed that none of the HCV-positive patients had PCT, a commonly encountered skin disorder among anti-HCV positive patients in the western world. Recently, mutations in the gene associated with hereditary hemochromatosis have been associated with sporadic and familial PCT, suggesting that inheritance of hemochromatosis alleles may be a susceptibility factor for the development of the disease. This may explain the absence of PCT in our previous study, which is in agreement with the study by Raslan et al.

Role prevalence of HCV genotypes. The genotypes 1, 2, and 3 are predominantly reported in the Americas, Europe and Asia while genotype 4 is found commonly in the Middle East, Egypt, central and west Africa. The region wise prevalence of genotypes include 1b and 2 (Southern Europe), 1a (USA, Northern Europe), 3 (Indian subcontinent), 4 (Africa, Middle East), 5 (South Africa), and 6 (South East Asia). According to the few existing studies in KSA, the most prevalent genotype in the Western Province and probably in the whole Kingdom was genotype 4, followed by genotypes 1a and 1b. Genotypes 2a/2b, 3 and 6 were rarely found; genotype 5 was seen only in the Western province. Previous studies have reported that genotype 1b poses an enhanced risk of disease progression to cirrhosis as well as malignant hepatoma. Studies in KSA suggest an increase in anti-HCV antibodies in apparently healthy Saudis with an increase of 5% in subjects aged >50 years. The range of anti-HCV in the Saudi population (2.2-5%) was found to be higher than many Western countries. Shobokshi et al. showed no differences in distribution patterns of genotypes between gender and age in KSA. It was indicated that there was an emergence of subtype 2a/2c in the Eastern region of KSA and at least 86% of chronic HCV cases are infected with genotypes 1 and 4. Al-Traif et al. reported that at least 64.5% Saudi HCV patients to be infected with genotype 4 followed by genotype 1 (30.6%). The latest study available from KSA is by Halawani et al. showed that approximately 12% of subjects positive for anti-HCV antibodies and 62.5%...
of subjects tested positive for HCV-RNA, and 80% of these patients had type 4 genotype. Subtyping showed that a significant majority of the type 4 genotype were of the HCV subtype 4a, followed by 4c and 4b genotypes. In an interesting and significant study from 2008 to 2011 conducted on 15323 liver disease patients in KSA showed anti-HCV detected in 7.3% of tested sera and 48.4% of HCV infected patients showed virus clearance and genotypes 1 and 4 were detected and type 4 was the predominant HCV genotype.75

There is an urgent need for case-controlled studies that take into consideration all confounding factors including age, gender, disease history, and so forth to better understand the role of HCV infection in causing skin symptoms. In addition, there is a lack of evidence available on understanding the geographic distribution of common genotypes across all the provinces of KSA and identification of high risk groups across this region. It has been shown by Zekri et al.,76 that infection with genotypes 1a and 4 could pose a risk factor for subsequent development of hepatocellular carcinoma.

Although there are a number of reports available from other countries investigating the prevalence and extent of association between HCV infection and various skin disorders, only few studies have been conducted in KSA where the HCV incidence is on rise.72,74 Most of the studies have focused on investigating the pattern of skin diseases in a certain region or a pre-defined cohort of patients.75-80 More recently, HCV infection has been associated with LP, and therefore screening of LP patients for aspartate aminotransferase, alanine aminotransferase, and anti-HCV antibodies for early diagnosis of HCV infection was recommended.81 Many additional studies and comprehensive data regarding the prevalence of HCV infection among the various dermatological patients in KSA are needed. Therefore, awareness and immediate recognition of dermatological manifestations is of paramount importance in facilitating early diagnosis and offering better treatment.

In conclusion, HCV infection occurs worldwide and the skin is the second most frequently targeted organ after the liver; dermatosis is often the only clinical evidence of the underlying disease. Therefore, it is vital to carefully examine skin manifestations for early diagnosis and management of HCV infection. Different HCV genotypes may have different effects on the cutaneous manifestations of HCV infection. There is little information available for the geographical distribution of different HCV genotypes across the whole Kingdom.

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