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Original Article

Mucocutaneous manifestations in hepatitis C patients

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Abstract

Objective To determine the frequency and nature of mucocutaneous manifestations in hepatitis C virus (HCV) positive patients.

Methods Two hundred and five HCV positive patients presenting at the outpatient and inpatient departments of Services Hospital, Lahore were evaluated for mucocutaneous manifestations. Relevant data regarding history, clinical examination including cutaneous system and investigations were documented and analyzed.

Results Mean age of patients was 36.6±11.0 years. There were 84 (41%) males and 121 (59%) females. 73.7% cases were exposed to antiviral therapy. Dermatological manifestations were present in 88.3% patients with HCV infection. Pruritus was the most common finding seen in 39.5% followed by hyperpigmentation of skin 34.1%, lichen planus 18%, lingual/buccal pigmentation 13.2%, melanonychia 12.7% and urticaria 6.8%. Less frequent features were palmar erythema, photosensitivity and cutaneous vasculitis.

Conclusion Dermatological manifestations may appear as an earliest sign of hepatitis C infection. Therefore, vigilant detection and careful investigation can prevent the complications and further spread of this dreadful disease.

Key words
Hepatitis C, mucocutaneous manifestations, extrahepatic manifestations.

Introduction

Hepatitis C is a global health issue caused by an RNA virus i.e. HCV.[1] Around the world more than 200 million persons are suffering from hepatitis C with the prevalence of approximately 3.3%.[2] According to WHO, Pakistan is included in the countries with higher rates of infection i.e. 4.8%.[1]

Hepatitis C causes acute infection less commonly and is a chief source of chronic hepatitis which may progress slowly to cirrhosis and hepatocellular carcinoma (HCC). Apart from hepatic signs and symptoms, numerous extrahepatic manifestations are also associated with it; involving the nervous, renal, gastrointestinal, muscular systems, bones and skin.[3,4] Dermatologic manifestations that tend to occur most commonly with HCV are lichen planus, pruritus, cryoglobulinemias and porphyria cutanea tarda.[4,5] Less frequent features include urticaria, erythema multiforme, polyarteritis nodosa, Sjogren's syndrome, erythema nodosum, purpura, Behcet's syndrome, acral necrolytic erythema, psoriasis and vitiligo.[4,6] Skin findings are also seen in

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chronic liver disease due to hepatitis C. These are clubbing, leukonychia, discoloration of skin and spider nevi. Furthermore, cutaneous manifestations particularly pigmentary changes of tongue, oral lichen planus and alopecia are associated with antiviral treatment for HCV infection.[4]

Majority of the patients with HCV infection show no symptoms for a long time until they develop serious complications which can lead to morbidity and mortality. Skin lesions may appear as the first or sole manifestation of hepatitis C which if detected by sharp and intelligent observation can lead to early management and avoidance of the life threatening complications.

Methods

The study was conducted in the outpatient and inpatient departments of Services hospital, Lahore. Hepatitis C positive patients of any age and gender were enrolled in the study. The diagnosis was confirmed by ELISA and/ or PCR. All patients were included irrespective of the duration and severity of the disease. HCV patients on or with history of antiviral treatment and those without history of treatment were considered.

Patients who were both hepatitis C and hepatitis B positive or had any other etiology for liver disease were excluded from the study. Systemic diseases like chronic renal failure, diabetes mellitus, rheumatoid arthritis or other autoimmune disorders were also excluded.

Informed consent was taken from all patients who were enrolled in the study. Detailed history, clinical examination including cutaneous system and relevant investigations were carried out. All the information was recorded on a proforma and the data were analyzed thereafter. Frequency of various mucocutaneous manifestations in hepatitis C patients was documented.

Results

A total of 205 patients having positive hepatitis C virus were studied. Male patients were 84 (41%) and female were 121 (59%) representing the male to female ratio of 0.7:1. Age ranged from 16 to 65 years with the mean age of 36.6±11.0 years. The highest number of patients i.e. 123 (60%) was in the age group of 30-49 years. The age group of <18 years comprised of the least number of cases i.e. 3 (1.46%). 184 (89.8%) patients were married and 21 (10.2%) unmarried. 151 (73.7%) patients had previously received or were receiving the antiviral therapy comprising of interferon alpha plus ribavirin whereas 54 (26.3%) were not on treatment.

Dermatological features were exhibited in 181 (88.3%) patients. The frequencies of various cutaneous manifestations are displayed in **Table 1.** The most frequently occurring manifestation was pruritus found in 81 (39.5%) patients Majority of the cases had pruritus without the evidence of skin lesions while only few showed the excoriation marks distributed over the trunk, arms and legs. Change in skin colour was noticed in 77 (37.6%) patients. Out of these, hyperpigmentation was present in 70 (34.1%) and yellowish discoloration as a sign of jaundice in 7 (3.4%) cases. Hyperpigmentation was generalized and mild to moderate in intensity.

Lichen planus (LP) was observed in 37 (18%) patients. Out of these, there were 3 patients who had itchy, purplish papules and plaques predominantly over limbs, 2 had generalized LP and 32 had involvement of oral cavity only. In most of the cases oral LP was manifested as

Table 1 Dermatological manifestations in hepatitis C patients (n=205).

Cutaneous finding	*N (%)*
Pruritus	81 (39.5)
Pigmentary changes	77 (37.6)
Lichen planus	37 (18)
Lingual/ buccal pigmentation	27 (13.2)
Urticaria	14 (6.8)
Leukonychia	13 (6.3)
Palmar erythema	6 (2.9)
Photosensitivity	5 (2.4)
Vasculitis	4 (2)
Spider nevi	4 (2)
Clubbing	3 (1.5)
Telangiectasia	3 (1.5)
Schamberg's disease	2 (1)
Prurigo	1 (0.5)
Vitiligo	1 (0.5)
Aphthous ulcer	1 (0.5)
Porphyria cutanea tarda	1 (0.5)
Splinter hemorrhages	1 (0.5)

Table 2 Hair changes in hepatitis C patients (n=205).

Hair changes	*N (%)*
Diffuse hair loss	41 (20.0)
Androgenic alopecia	6 (2.9)
Seborrhea	4 (2)

Table 3 Nail changes in hepatitis C patients

Nail change	*N (%)*
Melanonychia	26 (12.7)
Onychomycosis	2 (1)
Brittle nails	2 (1)
Koilonychia	2 (1)
Traumatic changes	2 (1)

white coloured streaks on the buccal mucosa while in others as painful erosive oral lesions.

Urticaria was identified in 14 (6.8%) patients. Other less frequent cutaneous findings noted were palmar erythema in 6 (2.9%), photosensitivity in 5 (2.4%), cutaneous vasculitis in 4 (2%), spider nevi in 4 (2%), clubbing in 3 (1.5%), telangiectasias in 3 (1.5%), Schamberg's disease in 2 (1%), splinter hemorrhages in 1 (0.5%), aphthous ulcer in 1 (0.5%), porphyria cutanea tarda in 1 (0.5%) and vitiligo in 1 (0.5%) of the patient. Melasma, eczema, xerosis, acne vulgaris, tinea pedis, tinea corporis, hyperhidrosis, lichen simplex chronicus, senile comedones and chill blains were also seen.

Manifestations specific to hair were diffuse hair loss, androgenic alopecia and seborrhea as shown in **Table 2**. Findings particular to nail disorders were onychomycosis, melanonychia, koilonychia and brittle nails as listed in **Table 3**. Regarding mucosal findings, blackish pigmentation in oral mucosa was observed in 27 (13.2%) patients. It was distributed on the lingual mucosa predominantly on lateral aspects in 19 (9.3%) cases while in 5 (2.4%) it was present only on the buccal mucosa. Involvement of both the buccal and lingual mucosa was found in 3 (1.5%) cases. Candidiasis (2.9%) was also noted.

Discussion

Chronic liver disease is frequently caused by hepatitis C virus infection throughout the world. It has a long and subclinical course may be with extrahepatic manifestations, before developing complications. Skin findings constitute an important part of these non-hepatic manifestations.[7]

In our study, demographic data showed 59% female and 41% male patients. This is in concordance with the 57% and 58% females seen in studies conducted by Asim *et al.*[5] and Soylu *et al.*,[7] respectively. Whereas Raslan *et al.*[8] found more number of male patients (67%). This female preponderance might be attributed to the fact that due to pregnancy complications they are more exposed to blood transfusions, parenteral drug administrations and caesarian sections in addition to be the subject for body piercing.

In the present study, largest age group is from 30-49 years, which is similar to the epidemiological study data of hepatitis C in Pakistan,[9] as well as, clinical study from this region.[6] The mean age of hepatitis C patients in the current study was 36.6±11.0 years. Various studies from Korea,[10] Egypt[8] and Turkey[7] revealed the mean age as 55.4, 46.95 and 51 years, respectively. Alarmingly, this might indicate that HCV is infecting the younger individuals in our region.

The current study demonstrated the dermatological manifestations in 88.3% of HCV-infected cases. In other studies 80% cases were detected to have skin disorders by Soylu *et al.*[7] and 71% by Raslan *et al.*,[8] respectively. While prospective studies performed by Cacoub *et al.*[3] and Paoletti *et al.*[11] found HCV-related cutaneous disorders in 17% and 12.5% patients, respectively. This variation could be due to racial, genetic and cultural differences in addition to variable exposure to risk factors.

Pruritus was the commonest cutaneous manifestation seen in 39.5% of our patients. Asim *et al.*[5] reported pruritus in 35% of cases. Another study described 50% cases of pruritus in Turkey[7] while Azfar *et al.*[6] found 15.9% in their study. In a multicenter study, Cacoub *et al.*[3] revealed 15% of cases of HCV with pruritus. Similar to our finding, all these studies mentioned pruritus as the most common skin finding in HCV positive patients. In contrast, Paoletti *et al.*[11] examined 96 patients of hepatitis C prospectively for 3 years and found pruritus in only 1.04% patients. Several mechanisms can explain the itch in hepatitis e.g. bile salts in skin,[12] cholestasis, direct effects of hepatitis C virus or related to interferon treatment.[13]

Hyperpigmentation was found in 34.1% of patients in our study. Generalized hyperpigmentation was seen in 6% of HCV cases after ruling out other causes of pigmentation by Azfar *et al.*[6] Willems *et al.*[14] described two dark-skinned chronic hepatitis C patients who developed hyperpigmentation of skin and tongue. They were on antiviral treatment, as well. Similar results were also noted by Gurguta *et al.*[15] in their study on non-Caucasian patients. Another striking finding in the current study was the presence of blackish pigmentation in the oral mucosa in 13.2% of patients, most commonly on the tongue distributed laterally. Tongue hyperpigmentation was noted by Aguayo-Leiva *et al.*[16] during interferon-alpha and ribavirin therapy. Lingual pigmentation was seen by Amir *et al.*[17] in 48% cases receiving antiviral therapy. This may be explained by the fact that 73.7% of HCV patients in our study had received or were receiving a combination of interferon alpha and ribavirin; therefore the specific lingual pigmentation might be the result of antiviral therapy.

Lichen planus was seen in 18% patients in our study. The relationship between LP and HCV is controversial. Various studies have reported the association of chronic liver disease and lichen planus, particularly oral LP with 1-4% of prevalence rate.[18] Whereas a study in Indian subpopulation showed no association between viral hepatitis and oral LP.[19] Frequency of LP in HCV positive patients in a study by Cacoub *et al.*[20] was found to be 0.9%. Soylu *et al.*[7] gave a value of 4% whereas 2% was described by Paoletti *et al.*[11] The exact etiology of HCV related LP is not known but can be hypothesized that T cell-mediated immunity against hepatitis virus initiates the disease.[4]

Urticaria can be a skin manifestation related to HCV. A case-control study by Cribier *et al.*[21] noted no significant association between chronic

urticaria and HCV. 12.5% cases of urticaria were found to be HCV positive in a study conducted by Malik *et al*.[22] We noted a frequency of urticaria as 6.8% in HCV in our study.

Cutaneous vasculitis has been related to Hepatitis C infection. Raslan *et al*.[8] found 2.6% of vasculitis patients out of 155 HCV positive cases which is almost similar to our finding of 2% vasculitis.

Nail changes can provide additional information and aid in the diagnosis of liver disease. In our study, the frequency of nail changes was found to be 16.6% with melanonychia being the commonest in 12.7% patients followed by onychomycosis and other findings. Salem *et al*.[23] recorded the nail abnormalities in patients with liver disease and found onychomycosis as the most common nail finding in 18% of cases followed by others. Etiology of nail plate disorders is by the involvement of nail matrix by disease or the therapeutic drugs.[24]

Hair disorders were also detected in 24.9% of HCV positive cases in present study. Alopecia was reported as a side effect of antiviral therapy in multiple studies.[25,26]

Conclusion

Dermatological manifestations may appear as an earliest sign of hepatitis C infection. Therefore, vigilant detection and careful investigation can prevent complications and further spread of this dreadful disease.

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