

An Evaluation of Frequency and Distribution of Cutaneous Manifestation in Patients of Hepatitis C Virus and its Correlation with Cardiac Manifestations

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Abstract

Background: Hepatitis C virus infection is a major health care concern worldwide but more so in developing countries like Pakistan, 170 million people have chronic hepatitis C virus infection. Which represents the 3% of global prevalence rate. Most patients with acute and chronic hepatitis C virus infection are asymptomatic and may remain oblivious of their disease for long time due to its indolent and silent course. Chronic

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hepatitis C virus infection may be associated with numerous extra hepatic manifestation and after liver skin could be the 2nd main target organ for many dermatologic manifestations and may be the 1st clue to the underlying HCV infection and may served as early marker of potentially fetal chronic liver disease and its complications.

Objectives:

- ✓ To determine the frequency and distribution of various dermatologic manifestation in patients with H and its consequent impact on development of heart disease.

Material and Methods: In this cross – sectional study conducted at Mayo Hospital, Lahore, the data was collected through consecutive sampling over a period of three years from 402 patients. These were found HCV positive during routine investigation. All patients gave a complete history regarding clinical features, cardiovascular risk factors profile and special history regarding dermatologic manifestation associated with HCV infection was inquired into. Detailed examination was done to see any evidence of skin manifestation. SPSS 15 was used for data management and analysis. Tabulation and Chi-square test were constituents of analysis.

Results: Out of 402 patients who were diagnosed to have Hepatitis C, 218 (54.2%) were males and 184 female the highest percentage (269; 66.9%) patients

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were more than 40 years of age with mean age 47.6 ± 13 years. 371 (92.3%) patients belonged to poor socioeconomic class, 164 (40.8%) patients were hypertensive, 129 (32.1%) were diabetic, 45 (11.2%) had a family history of Ischemia and 84 (20.9%) patients were smokers. 107 (26.6%) patients had various cutaneous manifestations (pruritis 10.69%, pruritus plus purpuric eruption 13.6%, isolated purpura was found in 1.7% and Eczema in 0.71%). Cutaneous manifestations were most common among, smokers, hypertensive, obese and patients having low socioeconomic status and suffering from Ischemic heart disease.

Conclusion: Overall higher frequency of cutaneous manifestation was observed in patients with positive serology for Hepatitis C virus infection and suffering from Ischemic heart disease, Hypertension and obesity along with low socioeconomic group and were habitual of smoking as compared with those who were HCV positive but not having associated these co-morbidities. Hepatitis C virus is suggested and must be considered in the differential diagnosis of these patients to avoid missing dis-important but occult factor in the clinical diagnosis of the skin diseases in appropriate setting.

Key words: HCV, IHD, CLD.

Introduction

Hepatitis C virus (HCV) has become a major cause of post-transfusion and sporadic non-A, non-B chronic hepatitis throughout the world. The prevalence of hepatitis C varies from one place to another due to environmental and geographical differences.¹ Although in developed countries the prevalence of HCV is less than 3%, but in Pakistan this prevalence is higher ranging from 4 – 7%.² Various studies have shown that patients with positive HCV serology are at greater risk of developing hepatic complications like the development of cirrhosis and hepatocellular carcinoma (HCC). HCV is also considered to be a leading indication of liver transplantation round the globe because of its high prevalence.³ Serious attempts need to be taken to eradicate this virus and consequently to reduce the increasing mortality and morbidity rate due to HCV infection. Additionally, Hepatitis C virus infection also induces many extra hepatic manifestations often seen in one third of patients with chronic infection,⁴ such as mixed cryoglobulinemia, Prophyria cutanea tarda, leukocytoclastic, vasculitis, Lichen Planus and Sicca Syndrome.⁵⁻¹⁰ Dermatologic manifestaions are a classic

presenting complaint in patients with essential mixed cryoglobulinemia.¹⁰ Overall higher frequency of palpable purpura is reported in HCV anti body positive patients and is related to the serum cryoglobulin level.¹⁰

Cutaneous symptoms or findings relevant to HCV infection manifests in 24 – 28%⁹ of the patients seen by dermatologist and 15 – 20% in the general population and may be the first clue to the underlying HCV infection. Hepatitis C virus is suggested and must be considered in the differential diagnosis of these patients to avoid missing dis-important but occult factor in the clinical diagnosis of the skin diseases in appropriate setting.¹¹

The many dermatologic manifestations in HCV infection was classified according to disease with proven or suspected etiology or causation. Primary cutaneous manifestation results from direct inoculation of HCV virus in the skin, Lymphocytes, dendric antigen presenting cells and blood vessels and the classical example of this is Lichen Planus.¹⁰ Secondary cutaneous manifestations occurs when infection manifests in the skin due to epi phenomena resulting from the disruption of immune response. Leuckocytoclastic vasculitis due to cryoglobulinemia is the classic example.¹⁰ Tertiary dermatologic manifestation results from another organ failure infected by HCV infection.¹² These manifestation are non specific. Another category of skin manifestations has definite association with HCV but clear explanation is not there for example Prophyria cutanea tarda in patients with PCP. 70% patients are HCV positive. There may be neoplastic dermatologic manifestations is another type of extra hepatic finding.

Cutaenous findings may be related with treatment of HCV infection especially Interferon.^{8,13} Presence of different type of skin problems, during early course of HCV – Therapy, has been reported in Europe¹⁴ and Asia.¹⁵ The general incidence of cutaneous eruptions of interferon is 13 – 23%.¹⁶

Pruritis is the most common extra hepatic cutaneous manifestation occurring in 74% of the patients. The prevalence of skin manifestations varies from one geographic area to another, probably due to differences in viral, genetic or environmental factors.¹⁷ Various studies have shown that up to 40 – 74% of the patents with HCV infection may have 1 manifestation in the course of the disease.¹⁸

Timely recognition of these symptoms help in early diagnosis and treatment of disease. Many Cutaneous diseases can be diagnosed and treated earlier if

cutaneous manifestations are identified as these can be a crucial clue for presence of HCV and other liver diseases.¹² Various studies have demonstrated a number of skin rashes and skin diseases that are associated with HCV infection and anti-HCV treatments.¹³ In order to have an alteration of these manifestations in Pakistan, it is found that many patients with HCV suffer from skin problems that may become very severe. A dermatologist has a very crucial responsibility and must have awareness about this silent epidemic.⁶ Patients with hepatitis C that are treated with interferons most often present with cutaneous manifestations such as hyperkeratosis and vasculitis.⁸

The prognosis of the patients with dermatologic manifestation with Hepatitis C virus depends on the success of therapy of the underlying HCV infection. Eradication of the HCV infection is the key factor in controlling cutaneous manifestations and prevention of fetal potentially fetal chronic liver disease.

Though, few studies have been conducted in Pakistan regarding evaluation of occurrence of cutaneous manifestation and their relation with HCV patients, more comprehensive work needs to be done in this domain. Thus, the aim is to elaborate various perspectives of cutaneous manifestation in patients with HCV.

Objectives:

- ✓ To determine the frequency and distribution of various dermatologic manifestation in patients with HCV seropositivity.
- ✓ To establish any association between cutaneous manifestation and general biomedical profile of HCV patients.
- ✓ To establish any link between Hepatitis C virus associated skin findings and Cardiac problems like Ischemic heart disease and CMP.

Materials and Methods

Study Design

Analytical cross – sectional study design was employed for this study.

Setting

This study was carried out at the Cardiology Department, Mayo Hospital, Lahore, from January 2006 to December 2008.

Methods

Our study population comprised of 402 patients. Patients population was divided into 2 groups. Group – A included 301 cardiac patients who were found to have seropositivity for HCV for antibodies and were under treatment of ACS, Cardiac Failure or Syncope. Group-B there were 101 non cardiac patients and were under treatment for Acute HCV infection at Hepatitis C outpatient clinic. Patients with CLD, Hepatic-B and previously known to have skin disease were excluded from the study. A specially designed, well structured and pre-tested questionnaire was used to collect desired information. Data were collected after getting consent of the patients and ethical issues were considered during the entire study duration. Data was analyzed using SPSS 15.0. The frequency and demographic patterns of patients were described via cross tabulation, graphs and pie charts. Mean and standard deviation was shown in descriptive analysis, while chi-square was applied in inferential analysis.

Results

Out of 402 patients included in the study, 218 (54.2%) were males and 184 (47.8%) were females. This shows that people more than 40 years of age are comparatively at higher risk of developing Hepatitis C. The overall patients enrolled in this study ranged 15 – 76 years of age. The mean age of patients was 47.6 ± 13.0 years. The highest percentage (269; 66.9%) of patients was more than 40 years old, while only 7 (1.7%) of patients in this study were less than 20 years old.

371 (92.3%) patients belonged to lower socio-economic class that was, indeed, a great majority. Out of 402 patients, 164 (40.8%) patients were hypertensive, 129 (32.1%) were diabetic, 84 (20.9%) patients were smokers. While 272 (67.6%) patients had their weight above normal, out of these 272 patients 189(69.5%) were overweight while the rest were obese. The spouse of 14 (3.5%) patients had a history of Hepatitis C. 107 (26.6%) patients had at least one of the mentioned types of cutaneous manifestations.

Out of 402 patients, 107 (26.6%) had at least one type of skin problem. Among these 107 patients with skin manifestations, most common (54; 50.5%) skin problem among patients was mixed type having both generalized pruritis with pruritic red spots. While 43

(40.2%) patients had generalized pruritis and only a eczema was found in 3 (2.8%) patients (Table 1). few 7 (6.5%) had isolated pruritic red spots and ecze-

Table 1: Distribution of various types of skin problems among all patients with cutaneous manifestations.

Skin Manifestation and its Type		Frequency	Percentage (%)
Positive	Generalized pruritis with pruritic red spots	54	13.43%
	Generalized pruritis	43	10.70%
	Isolated pruritic red spots	7	1.74%
	Eczema	3	0.75%
	Total	107	26.61%

Table 2: Distribution of cutaneous manifestation among different variables studied

		Cutaneous Manifestation		Total	p-value
		Yes	No		
Gender	Male	50	168	218	0.027
	Female	57	127	184	
	Total	107	295	402	
Economic Status	Lower class	94	277	371	0.045
	Middle class	13	18	31	
	Total	107	295	402	
Hypertension	Yes	48	116	164	0.002
	No	59	179	238	
	Total	107	295	402	
Smoking	Yes	18	66	84	0.021
	No	89	229	318	
	Total	107	295	402	
Diabetes Mellitus	Yes	38	91	129	0.147
	No	69	204	273	
	Total	107	295	402	
Heart Disease	Yes	71	230	301	0.000
	No	36	65	101	
	Total	107	295	402	
History of HCV in spouse	Yes	5	9	14	0.035
	No	102	286	388	
	Total	107	295	402	

The distribution of these cutaneous manifestations was also studied. Out of these 107 patients with cutaneous manifestation 57 (53.3%) were females while 50 (46.7%) were males. 65 (60.7%) patients with skin

problems were more than 40 years of age. A great majority (94; 87.9%) of patients with cutaneous manifestations belonged to poor socioeconomic status, 18 (16.8%) patients had a smoking history 82 (76.7%)

Table 3:

Frequency of different type of heart diseases.

Heart Disease	No.	% age	P-value
Ischemic Heart Disease	224	74.4	0.000
Valvular Heart Disease	22	7.3	0.003
Infective Endocarditis	2	0.7	-----
Cardiomyopathy	34	11.3	0.170
Complete Heart Block	10	3.3	0.011
Congenital Heart Disease	3	1	0.567
Mixed Heart Diseases	4	1.3	-----
Peripheral Vascular Disease	2	0.7	-----
Total	301	100	

patients had body mass index (BMI) above normal. Only 38 (35.5%) diabetic patients were found to be suffering from at least one of the skin problems but were not statistically significant (p-value = 0.147). Out of 107 patients with cutaneous manifestations, 71 (66.4%) were diagnosed to have at least some heart disease depicting the fact that cutaneous manifestations may be the hallmark of vasculitis and its subsequent cardiac manifestations (Table 2).

Among cardiac patients with sero positivity for Hepatitis C virus infection 224 (74.4%) were ischemic heart disease patients, cardiomyopathy (8.5%), valvular heart disease (5.5%) and complete heart Block (2.5%) and others. Also, significant association was found between cutaneous manifestation and different types of heart diseases (p-value = 0.012) and the highest percentage enrolled and found highly significant, was of IHD patients (p-value = 0.000). Cutaneous manifestation had significant association with valvular heart disease and complete heart block while no statistical significance was observed with cardiomyopathy and congenital heart disease. Both patients of Infective Endocarditis had the skin problems while none of the patients with Peripheral Vascular Disease and Mixed Heart Diseases suffered from any kind of skin problem. Thus, because of lying in merely yes or no category of skin problem, these three diseases did not fulfill the criteria of Chi-square utility. Hence, p-value for these diseases could not be given (Table 3).

Chi-square test was also applied for evaluation of any possible association between cutaneous manifesta-

tion with different observations of patient's biomedical profile and in particular, with development of heart disease. Hence, highly significant association was found between skin manifestations and occurrence of overall heart problem as well as Ischemic Heart Disease (p-value 0.000). Moreover, presence of skin problem in HCV patients had a significant association with female gender (p-value 0.027) and poor socioeconomic status (p-value 0.045). Additionally, significant association was established between cutaneous manifestations and smoking (p-value 0.021), hypertension (p-value 0.002), Body Mass Index (BMI) (p-value 0.001), age (p-value 0.003) and history of HCV in spouse of the patient (p-value 0.000).

Discussion

Hepatitis C has become the most common and foremost cause of acute and chronic liver disease. The test for hepatitis C antibody was available, for the very first time, in 1989, when unexplained cases of chronic hepatitis were labeled as non-A and non-B.¹⁹ In a study conducted by Umar et al. it was shown that male to female ratio was almost equal in HCV patients². Almost similar result was observed in our study, where male to female ratio was 1.18:1. Yet, the distribution of cutaneous manifestation in HCV patients had a positive association with gender. In many epidemiological studies, it is demonstrated clearly that HCV infection is relatively rare and infrequent in people of

younger age, especially below age of 20 years and is more prevalent in people who are above 40 years of age.²⁰ In our study too, only 7 (1.7%) of patients with HCV were present in age category of below 20 years. Moreover, in our study the maximum number (269; 66.9%) of patients were more than 40 years old depicting the fact that disease becomes more active after the age of 40 years. The frequency and incidence of cutaneous manifestation varies from one geographical area to other and depends on various genetic, environmental factors and differences in study criteria. According to the results of one study the frequency of dermatologic manifestation was found to be 45.8%, which was higher than reported by another study.¹⁹ In our study 26.6% patients who were sero positive for HCV infection had cutaneous manifestation. Though this percentage is almost similar to what was observed in another study where it was found to be 24 – 28%.¹⁵ This difference may be due to genetics, geographical, racial, study criteria or other factors.

In our study the most common type of skin lesion was mixed type generalized pruritis with red spots and pigmented purpuric eruption. In a study conducted by Raslan et al. the similar results were presented, where pruritis was found to be most common skin problem in patients.²¹ In addition to generalized pruritis (10.70%) and isolated pruritic red spots (1.74%) were also presented in some patients. Eczema was found in 3 (2.8%) patients with HCV. The presence of eczema is also supported by other studies conducted to evaluate the cutaneous manifestations in HCV patients.²² In our study higher frequency of cutaneous manifestation was observed in patients with history of smoking, hypertension, obesity and cardiac problem. Many studies have internationally been conducted and established the relationship of skin problems with consequent development of heart disease. These heart diseases may constitute coronary artery disease (CAD), cardiomyopathy, peripheral vascular disease and infective endocarditis.^{23,24} Our study showed the similar results in which 26.61% patients who suffered from skin manifestations were also established to have ischemic heart disease, cardiomyopathy and other cardiac problem as mentioned in table 3 and had highly significant association with different types of skin problems as well ($p = \text{value } 0.000$).

The possible mechanism for the development of vasculitis / coronary artery disease and cardiomyopathy may be the direct colonization of the vessel wall or myocardium²⁶ by pathogen leading to viral

replication in extra hepatic size and its related damage. Or by stimulation of an inflammatory cascade causing changes in the vessel wall such as thickening, weakening and narrowing. HCV related cryoglobulinemia and immune complex mediated inflammation²⁷ could be associated with endothelial damage and may account for coronary artery atherosclerosis and coronary dissection²⁸ leading to acute coronary syndrome.²⁹

Conclusion

In our study pruritis and pigmented purpuric eruption were most common skin presentation and were significantly associated with Ischemic heart disease, hypertension and smoking. Occult pruritis and purpura may be regarded as early marker of potentially fetal chronic liver disease and may be the first clue to underline HCV infection.

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