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ORIGINAL ARTICLE

INTERSTITIAL PULMONARY DISEASE IN HEPATITIS C VIRUS PATIENTS

By

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Chronic hepatitis C virus infection has been reported in association with several extrahepatic manifestations. Included in this list is interstitial lung involvement. This study aimed to elucidate the association of HCV infection with interstitial pulmonary involvement and to investigate the relationship of severity of hepatic affection and respiratory functional and radiological changes among involvement. Thirty patients with proved hepatitis C virus (HCV) infection from the outpatient clinic of tropical department of Kasr El-Aini hospital were enrolled in this study. High resolution CT (HRCT) chest was performed to all the patients. Pulmonary changes were detected in HRCT of 14 patients (46.6%). Lung spirometry was done to all of them. FVC%, and FEV1% were abnormal in 6 patients (20%), FEF25-75% were abnormal in 3 patients (10%). DLCO was measured in 23 patients and was abnormal in 3 patients (13%). Liver biopsy results according to the fibrosis stage (METAVIR fibrosis grading scale) revealed to be grade I in 11 patients (36.7%), grade II in 9 patients (30%), grade III in 8 patients (26.7%) and grade IV in 2 patients (6.7%). The study showed significant inverse correlation between viremia level with DLCO% pred as well as significant direct correlation between liver fibrosis stages with AFP, FEV1/FVClevel and HRCT score in the studied patients. In addition to this AFP was directly correlated with the HRCT score. Otherwise, there was no significant correlation between the following variables: HRCT score and pulmonary function tests, Liver fibrosis with FEV1%, FVC%, DLCO% and viremia level, Alphafetoprotein with pulmonary function tests and viremia level in the studied patients & Age with pulmonary function tests, AFP, liver fibrosis, and viremia level and HRCT chest.

Keywords: *HCV, Interstitial pulmonary disease, PFT, HRCT.*

INTRODUCTION

Hepatitis C virus (HCV) is a common infectious agent, and it is estimated that 3% of the world population are infected with HCV.(1) HCV being both a hepato and lymphotropic virus can represent a chronic stimulus for the immune system.(2) In the general population of HCV positive patients the appearance of various organ involvement can be related to different immunological factors namely various

autoantibodies and immune complex production secondary to B lymphocyte expansion.[3]

Since HCV is well known to induce chronic inflammation and fibrosis in the liver, it was thought that HCV may play a similar role in the lung and be involved in the pathogenesis of pulmonary fibrosis.[4] An association between HCV infection and IPF was initially supported by seroepidemiological data, which revealed a higher prevalence of anti-HCV antibodies in patients with IPF.[5] Onset of symptoms following a viral infection or common cold in some patients suggests that development of the disease may be due to the injury related to the infection. There is evidence that hepatitis C virus, Epstein-Barr virus (EBV), and adenoviruses may be responsible for the fibrosis.[6]

The aim of this study is to elucidate the association of HCV infection with interstitial pulmonary involvement and to investigate the relationship of severity of hepatic affection and respiratory functional and radiological changes.

SUBJECTS AND METHODS

This study included 30 patients diagnosed to have HCV infection. They were chosen from the outpatient clinic of Tropical department, Kasr El-Aini hospital, Cairo University.

The following were the exclusion criteria:

- Patients with previous diagnosis of decompensated cirrhosis.
- Patients with manifestations of congestive heart failure.
- Patients with lung diseases other than interstitial pulmonary disease.
- Patients with chronic infections, renal or connective tissue disorders.
- Patients receiving medications with a potential to cause pulmonary alterations.
- Patients with occupational risk factors for interstitial lung disease.

All patients were subjected to the following:

1. Thorough history taking & clinical examination.
2. Resting spirometry (V-max 229 pulmonary function sensor medics).
3. Resting carbon monoxide diffusing capacity (DLCO) using single breath technique. (NB: 7 patients were unable to perform the test).
4. High resolution CT chest (Somatom Plus-S (siemens-Germany) CT unit) Patients were examined at the Radiodiagnosis department, Kasr El- Aini hospital.

   For evaluation of interstitial involvement with HRCT, the method described by Remy-Jardin et al in 1994 was used.[7] HRCT scans were evaluated for the presence, distribution, and extent of the following signs: [a] ground-glass attenuation, [b] nodular areas of high attenuation, [c] consolidation, [d] linear areas of high attenuation, classified as nonseptal lines, [e] septal lines, [f] honeycombing, and [g] architectural distortion.

   Ground-glass attenuation was defined as areas of increased attenuation without obscuration of the underlying vessels and bronchi. Nodular areas of high attenuation were defined as round areas of soft tissue attenuation 1-20 mm in diameter. Septal lines were defined as regular or irregular thickening of the interlobular septa whereas nonseptal lines were defined as linear areas of high attenuation distinct from interlobular septa or bronchovascular bundles. Honeycomb cysts were defined as localised areas of decreased attenuation with well-defined walls. Architectural distortion was considered present when fissures and hila were displaced or the secondary pulmonary lobule, bronchi, or vessels were distorted.

   Extension of the involvement was assessed independently for each of the three zones of the thorax defined as follows; the upper zones were above the level of the main carina, the middle zones were between the level of the main carina and the inferior pulmonary veins,

and the lower zones were under the level of the inferior pulmonary veins. HRCT scores in the upper, middle, and lower pulmonary zones were determined by visually estimating the extent of the disease in each zone. The HRCT score was based on the percentage of pulmonary parenchyma that showed evidence of each recorded abnormality, and was estimated to be 5% of parenchymal involvement: 25% and below as 1 point, 26%-50% as 2 points, 51%-75% as 3 points, 76% and above as 4 points. The scores for each zone were then added to obtain a global extent score, ranging from 0 to 12, and referred to as the HRCT extent score of each HRCT abnormality. A total score of pulmonary involvement was obtained by summation of the global extent score of all HRCT abnormalities, ranging from 0 to 84, which was the feature referred to as the overall HRCT of disease severity.

5. Serology for HCV
6. Abdominal Ultrasound.
7. Liver biopsy Technique

Staging to detect the degree of fibrosis according to METAVIR score:

- F 0: No fibrosis
- F 1: Portal fibrosis
- F 2: Bridging fibrosis, slight
- F 3: Bridging fibrosis, marked
- F 4: Cirrhosis. [8]

8. Statistical methods:

Patients' data were tabulated and processed. Categorical variables were expressed by number and percent. Quantitative variables were expressed by mean and standard deviation (SD) and compared by t-student test. Correlation between quantitative variables was done by Pearson or Spearman correlation when appropriate. In all tests, P value was considered significant if it was below (0.05).

RESULTS

Table 1. Demographic and clinical data of the studied patients.

Age:	
Mean±SD	43,46 ± 8,77years
Range	24-59 years
Sex:	
Male no. (%)	21(70%)
Female no. (%)	9 (30%)
Smoker no. (%)	10 (33.3%)
Non smoker no. (%)	20 (66.6%)
Pulmonary manifestations no. (%)	4 (13.3%)
Liver manifestations no. (%)	0
Extrahepatic manifestations no. (%)	3 (10%)

- Mean amount of cigarettes smoked was 200±126 (SD) pack/year.
- Regarding pulmonary symptoms, four patients (13.3%) complained of morning cough and expectoration of minimal amount of odourless sputum. Chest auscultation in these patients revealed vesicular breathing with prolonged expiration. These patients had history of cigarette smoking. Otherwise the

rest of the patients did not have any chest complaint and chest examination revealed to be normal.

- The duration and onset of HCV infection could not be ascertained as no one of the patients gave history of acute illness.
- Extrahepatic manifestations of HCV were encountered in 3 patients (Two of them (6.6%) complained of arthralgia and one patient (3.3%) complained of skin affection in the form of erythema nodosum and urticaria.

Table 2. Pulmonary function data of the studied patients.

No.	Fev1 % Pred	Fvc % Pred	Fev1/fvc % meas	Fef 25-75%	Dlco % pred
1	94	88	81	96	91
2	86	85	76	69	108
3	84	85	72	58	91
4	93	86	82	93	115
5	76	79	73	53	117
6	97	94	80	85	95
7	85	85	73	72	84
8	103	94	83	112	122
9	121	113	78	113	108
10	67	71	74	52	89
11	96	94	79	93	116
12	103	95	84	124	135
13	82	70	88	101	70
14	89	80	83	108	122
15	83	82	79	80	114
16	74	74	78	68	124
17	78	62	94	141	85
18	88	87	80	71	82
19	109	104	83	103	73
20	106	102	79	99	75
21	75	77	81	65	120
22	105	112	70	73	107
23	105	91	87	125	104
24	117	110	87.9	112	-
25	78%	77	78	77	-
26	91	88	86	24	-
27	121	100	100	197	-
28	85	85	75.3	77	-
29	142	131	77	147	-
30	106	94	92	128	-

Table 3. Statistical analysis of pulmonary functions data of the studied patients.

Pulmonary functions	Mean	Std. Deviation	Range
FVC%pred	89.83	14,598	63-131
FEV1%pred	94,63	16,812	67-121
FEV1/FVC%	81,11	6,756	70-100
FEF25-75%pred	90.6	26.9	35-147
DLCO%pred	102	18,585	70-135

Table 4. Percentage of cases with normal (>80%) and abnormal (<80%) Pulmonary function data.

	Abnormal (< 80%)		Normal (>80%)	
	No.	%	No.	%
FVC%	6	20%	24	80%
FEV1%	6	20%	24	80%
DLCO%	3	13.1 %	20	86.9%

Table 5. Pulmonary function test patterns in the studied patients.

	NO.	%
Normal Pulmonary functions	23	76.6%
Obstructive disorder	2	3.3%
Restrictive disorder	5	16.6%
Small airway obstruction	4	13.3%
Diffusion defect	3	13.1%

Results of HRCT chest:

- Interstitial pulmonary changes →14 patients (46.6%).
- Pulmonary changes other than interstitial affection → 9 patients (30%).
- No abnormality detected → 7patients (23.3%).
- Other findings were detected but were not included in the score being unrelated to the interstitial pathology. These were basal pulmonary congestion in 5 patients (16.6%), pleural thickening in 5 patients (16.6%), lung cysts in 6 patients (20%), areas of air trapping in 3 patients (10%) and emphysema in 1 patient (3.3%) patient.

Table 6. Results of HRCT chest of the studied patients and their scores as regards the presence and distribution of different manifestations of interstitial lung disease based on Remy-Jardin score.

No	HRCT score	HRCT
1	4	Bilateral groundglass attenuation in the lower lung zones,mild hepatomegaly.
2	0	No abnormality detected (NAD).
3	4	Bilateral lower zonal groundglass attenuation, right basal cystic changes and peripheral cicatricial emphysema Liver cirrhosis.
4	0	Basal pulmonary congestion.
5	0	Right upper lobe air trapping and right apical posterior pleural thickening.
6	0	NAD.
7	0	Right basal pleural thickening.
8	0	Bilateral basal pulmonary congestion.
9	2	Bilateral basal pulmonary congestion and non septal lines in the left middle and lower zones.
10	0	Left basal air trapping.
11	0	NAD.
12	0	NAD.
13	0	Left apical pleural thickening.
14	6	Hepatosplenomegaly. Portal hypertension,areas of high attenuation in bilateral lower lung zones,bilateral midzonal non septal lines and right apical subplueral cyst.
15	4	Bilateral groundglass attenuation in the lower lung zones,right retrosternal cyst &left basal cysts.
16	0	NAD.
17	1	Non septal lines in the left anterior lower lung zone.Liver is enlarged & fatty.
18	3	Groundglass attenuation in the left lower lung zone and anterior right lower zonal atelectatic band.
19	0	Left basal air trapping.
20	0	Basal pulmonary congestion and minimal right basal pleural thickening.
21	0	NAD.
22	2	Apical non septal lines and basal pulmonary congestion.
23	1	Bilateral basal tiny cysts and right basal non septal lines
24	2	Bilateral apical non septal lines and left apical lower lobe parenchymal cysts.
25	0	NAD.
26	3	Non septal lines in the left middle and lower zones.
27	0	Bilateral basal air trapping.
28	16	Areas of high attenuation in bilateral upper lung zones,groundglass attenuation in bilateral middle and lower lung zones and non septal lines in bilateral middle lung zones.
29	2	Bilateral lower zonal non septal lines and bilateral apical nodular pleural thickening.
30	4	Bilateral lower lobe groundglass attenuation, left basal (lateral) cysts and mild hepatomegaly.

Table 7. Detailed HRCT chest findings as a percentage regarding pulmonary changes of interstitial lung disease.

Pulmonary changes	Number of cases	Percentage
Ground glass attenuation	6	20%
Nodular areas of high attenuation	2	6.6%
Consolidation	0	0
Septal lines	0	0
Non septal lines	8	26.7%
Honeycoombing	0	0
Distortion	0	0

This table demonstrates that the non septal lines and the ground glass attenuation were the commonest findings.

The following figures are HRCT of some of the studied patients with interstitial pulmonary affection.

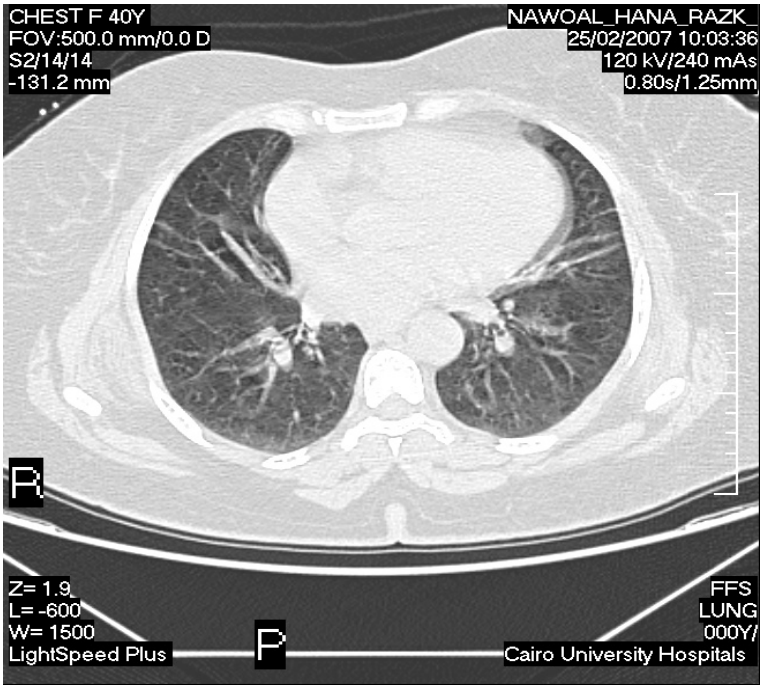

Fig 1. HRCT chest of case (no.28) A 51 year old female patient with HCV infection. She had no chest complaint and was a non smoker. This cut of HRCT of the chest showed bilateral areas of groundglass attenuation in the lower lung zones and the rest of the cuts showed bilateral areas of high attenuation in the upper zones, non septal lines and bilateral areas of groundglass attenuation in the middle lung zones. She took a score of 16.

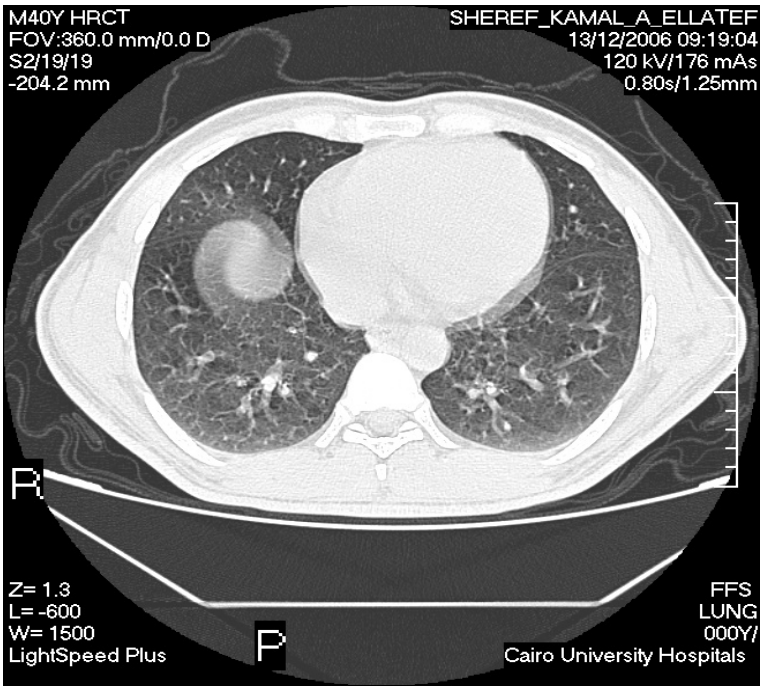

Fig 2. HRCT chest of case (no.30) A 40 year old male patient with HCV infection, non smoker. He had no chest complaint. This cut of HRCT revealed bilateral lower lobe groundglass attenuation. The rest of the cuts showed left basal (lateral) cysts. He took a score of 4.

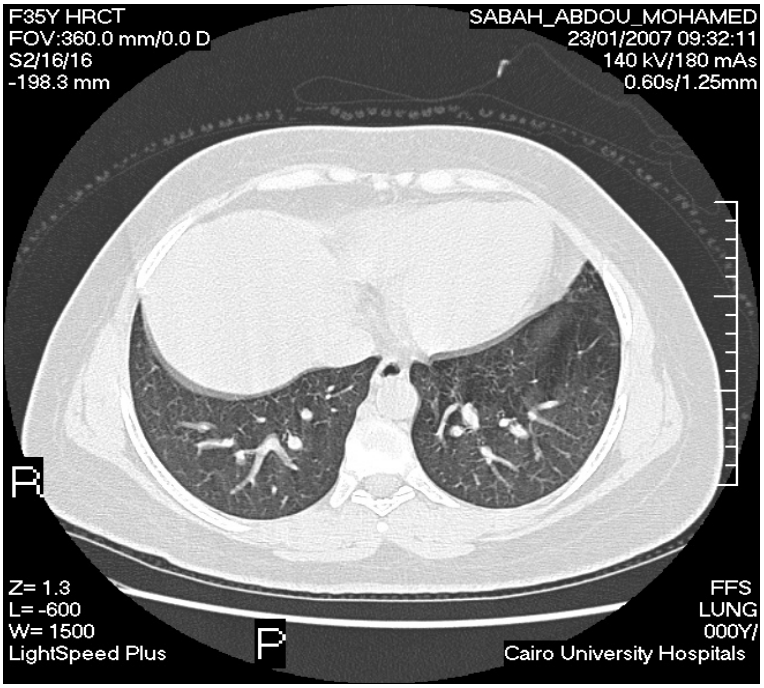

Fig 3. HRCT chest of case (no.18) A 32 year old female patient with HCV infection, non smoker. He had no chest complaint. This cut of HRCT revealed groundglass attenuation in the left lower lung zone. The rest of the cuts showed anterior right lower zonal atelectatic band. She took a score of 3.

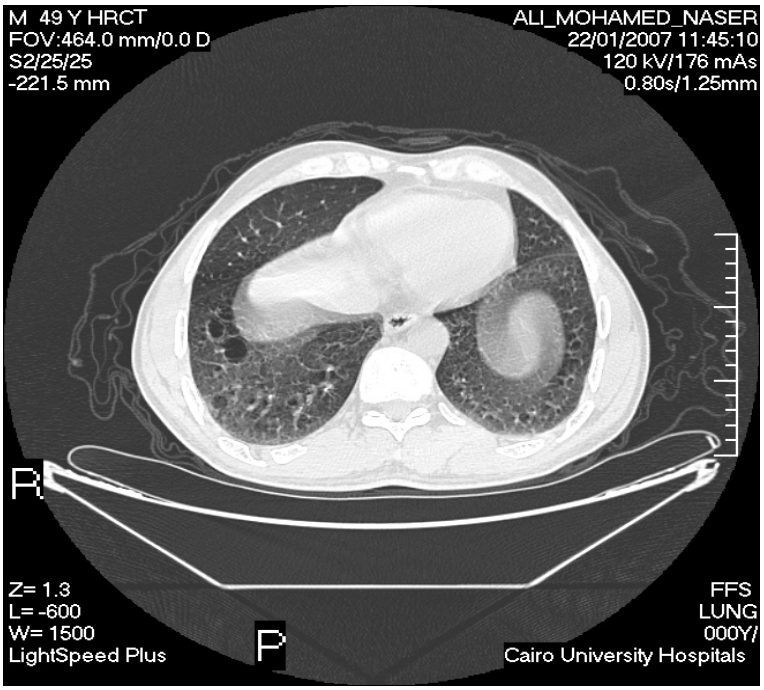

Fig 4. HRCT chest of case (no.3) A 48 year old male patient with HCV infection. Smoking index was 100. He complained of mourning cough & expectoration. Chest auscultation revealed vesicular breathing with prolonged expiration. This cut of HRCT revealed bilateral lower zonal groundglass attenuation and right basal cystic changes the rest of the cuts showed peripheral cicatricial emphysema. He took a score of 4.

Table 8. Correlations between liver fibrosis stages and pulmonary function tests.

	Correlation Coefficient	P value
FVC% pred	-,270	,149
FEV1% pred	-,049	,812
FEV1/FVC%	,527	,003 (s)
DLCO% pre	,011	,961

This table shows significant correlation between liver fibrosis stages and FEV1/FVC% values in the studied patients otherwise no significant correlation between liver fibrosis with FEV1%, FVC% and DLCO% were detected.

Table 9. Statistical comparison of pulmonary function data in patients with different grades of liver fibrosis.

	Minimal fibrosis Stage 1 and 2 (n=20)		Significant fibrosis Stage 3 and 4 (n=10)		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
FEV1% pred	95.9	19.48	92.1	9.96	0.57
FVC% pred	95.7	18.8	83.4	10.41	0.07
FEF25-75% pred	88.05	38.23	105.5	21.86	0.19
DLCO% pred	103	18.88	100.56	19.14	0.77

This table shows no statistical significance in all parameters.

Table 10. Correlations between liver fibrosis stages with AFP, HRCT chest and viremia.

	Correlation Coefficient	P value
AFP	,401	,031(s)
HRCT score	0.44	0.02 (S)
Viremia level	.096	.642

This table shows significant correlation between liver fibrosis stages with AFP level and HRCT chest score in the studied patient and no significant correlation between liver fibrosis with viremia level.

Table 11. Correlations between Alpha-feto protein levels and pulmonary function tests.

	Correlation Coefficient	P value
FVC%pred	-,225	,242
FEV1%pred	-,109	,575
FEV1/FVCmeas	,054	,783
DLCO%pred	-,364	,087

This table shows no significant correlation between AFP and pulmonary function tests in the studied patients.

Table 12. Correlations between Alpha-feto protein levels with viremia level and HRCT chest score.

	Correlation Coefficient	P value
Viremia level	.209	.315
HRCT score	0.39	0.04 (S)

This table shows significant correlation between AFP and HRCT chest score and no significant correlation between AFP and viremia level in the studied patients.

Table 13. Correlation between HRCT chest score and pulmonary function tests.

	Correlation Coefficient	P value
FVC%pred	,201	,297
FEV1%pred	,183	,343
FEV1/FVCmeas	-,028	,883
DLCO%pred	-,062	,778

This table shows no significant correlation between HRCT chest score and pulmonary function tests.

Table 14. Correlation between viremia level with pulmonary function tests and HRCT chest.

	Correlation Coefficient	P value
FVC%pred	-.236	.247
FEV1%pred	-.217	.286
FEV1/FVCmeas	-.081	.694
DLCO%pred	-.478(*)	.039(s)
HRCT	,022	,917

This table shows significant inverse correlation between viremia level and DLCO%pred.

Table 15. Correlation between the age with pulmonary function tests.

	Correlation Coefficient	P value
FEV1%pred	-.031	.876
FVC%pred	-.096	.629
FEV1/FVCmeas	-.326	.090
DLCO%pred	-.203	.364

This table shows no significant correlation between the age with pulmonary function tests.

Table 16. Correlations between age with AFP, liver fibrosis, and viremia level and HRCT chest.

	Correlation Coefficient	P value
AFP	.146	.468
fibrosis	.124	.530
Viremia level	.057	.792
HRCT score	0.27	0.18

This table shows no significant correlation between age with AFP, liver fibrosis, and viremia level and HRCT chest.

DISCUSSION

Hepatitis C virus (HCV) infection is an important public health problem worldwide. It is estimated that 3% of the world population is chronically infected with HCV.[9]

There has been very high prevalence rates of HCV reported in Egypt in the past (28%).[10] This was confirmed among 90 blood donors in Cairo, where 14.4% were anti-HCV positive by RIBA test.[11]

Then 26.6% among 188 blood donors and 22% among 163 donors were positive with both studies done in Cairo.[12]

Several reports have documented the association of HCV infection with extrahepatic phenomena, including cryglobulinaemia, glomerulonephritis, thyroiditis, sialadenitis and lichen planus. Within the last decade, interstitial lung involvement has also been integrated into this list.[13]

There are few studies about pulmonary involvement of chronic HCV infection. These have been done with small patient groups and results on the association between chronic HCV infection and pulmonary involvement could not be found from these studies.[14]

HRCT chest scanning, has replaced conventional chest radiography as the preferred imaging method for the ILDs due to its greater ability to visualize fine details within the lung.[15] HRCT chest has been found useful in the evaluation of ILDs in the following areas: identification of the presence of disease (often being abnormal when other studies are normal or only mildly impaired), evaluation of the extent of disease, characterization of the patterns of the disease, narrowing the differential diagnosis, as a guide to the site of biopsy, and assessing the clinical course of the disease and response to therapy.[16]

Lung spirometry and diffusion tests were done to the patients as assessment of ventilatory function and gas exchange is essential in the evaluation of patients with ILD.[17]

In the present study, abnormal results of HRCT and DLCO were obtained in 14/30 (46.6%) and 3/23 (13%) patients respectively. FVC%, and FEV1% were below 80% of predicted values in 6/30 patients (20%), FEF25-75% was abnormal in 3/30 patients (10%). These findings suggested a high rate of subclinical pulmonary affection in patients with HCV infection.[18]

In 2006, Rabie[19] investigated 30 patients with HCV infection. Lung spirometry was done to all patients. They found abnormal FVC in 10/30 patients, in FEV1 in 7/30 patients, and in FEF25-75 in 15/30 patients, respectively. The present results are in agreement with the results of Okutan et al.[20] in (2004) who studied thirty four patients with chronic hepatitis C virus (HCV) infection. Their HRCT findings revealed interstitial pulmonary involvement in 16/34 patients. They also found abnormal FVC%, FEV1% 9 and 8 patients out of 34 respectively. On the contrary to the present study findings DLCO% was decreased in 26/34 patients and FEF25-75 % was decreased in 15/34 patients.

Erturk et al.[21] in (2006) studied twenty patients with chronic HCV infection. They found abnormalities in HRCT in 8 patients (40%) all of them considered of mild fibrosis. FVC, FEV1/FVC and FEV1 values were abnormal in three (15%), 11 (55%) and five (25%) patients, respectively. DLCO% was reduced in 12 patients (60%) and a low DLCO/VA ratio was found in 8 of them. The mean DLCO (%) and DLCO/VA (%) ratios were 76.50±22.53 and 82.95±19.99, respectively. Also, they found that patients who had received specific anti-viral treatment had a tendency to have higher DLCO values as compared with untreated patients. (82.67±23.77 versus 67.25±18.10; $p > 0.05$). Moreover, DLCO/VA ratios were significantly higher in treated patients.

The controversy between the present study DLCO results and the previous two studies may be related to the duration of HCV infection as all their cases were chronic, while the duration of HCV infection of the present study could not be ascertained. Also, most of patients in the present study received antiviral treatment which may improve the results of DLCO. This is supported by Yamaguchi et al. in (1997) who demonstrated that T lymphocyte activation markers in BAL are reduced by IFN-treatment.Also, Manganelli et al.[22] in (1996) and Salaffi et al.[23] in (1996) reported an IFN-responsive subclinical T-lymphocyte alveolitis in patients with MC and HCV infection.

In the present study there was no significant correlation between HRCT score and pulmonary function tests Table 13. There are contradictory results in the literature about correlations between PFT and HRCT score in patients with pulmonary fibrosis.[20]

Ferri et al in (1997)[17] found that the severity of lung fibrosis expressed by score of HRCT is correlated with the reduction of DLCO. All their cases (8 patients) had clinical and radiological manifestations of IPF, while in the present study the selected cases were clinically free of manifestations of IPF.

Fernando and Flaherty in (2006)[24] stated that although unusual, normal pulmonary function tests cannot be assumed to exclude IPF in the presence of suggestive clinical or radiographic abnormalities. In agreement with the present result Okutan et al.[20] in (2004) found no correlation among HRCT, FVC and DLCO in patients with HCV infection.

In 1994, Remy-Jardin et al.[7] investigated the role of HRCT in determining disease activity and functional impairment in patients with sarcoidosis. Pulmonary function tests and HRCT were done to the patients. The study showed low correlation between the overall CT score of disease extent and functional parameters.

The absence of significant correlation between HRCT score and pulmonary function tests in the present study may be explained by the fact that the interstitial involvement that was encountered in the studied patients was not diffuse (i.e:did not affect the whole lung parenchyma).In addition to this all the studied patients who showed interstitial lung affection by HRCT chest had a low HRCT score i.e: mild interstitial affection.

As HCV infections generally follow a silent course and as they are rarely diagnosed at the acute phase, onset of the disease usually could not be determined.[25] So, duration of the disease was not investigated among factors that would possibly affect the development of pulmonary involvement. Age may indirectly be a sign of the duration of the disease, because duration of HCV infection may not be accurately determined.[20]

In the study of Okutan et al. [20] in (2004) HRCT score and PFT parameters were related with age. This was opposite to the present study where there was no significant correlation between age with pulmonary function tests, AFP, fibrosis, viremia level and HRCT.

The METAVIR scoring system and KHAI (knodel histological activity index) is known for the evaluation of liver parenchyma. In the present study liver fibrosis was assessed by the METAVIR scoring system and there was significant direct correlation between liver fibrosis stages with HRCT score in the studied patients. On the contrary to the present study findings Okutan et al. [20] (2004) found no correlation between liver fibrosis stage assessed by knodel histological activity index and HRCT score. However Okutan et al. [20] (2004) found inverse correlation between liver fibrosis stage and DLCO/VA. The present study showed opposite results as there was no significant correlation between the liver fibrosis and all pulmonary function tests. Although the two studies showed different results, however both results indicated that there is a relationship between the degree of liver fibrosis and the degree of interstitial lung affection in HCV infected patients.

The prevalence of elevated serum AFP varies from 10% to 43% in patients with chronic hepatitis C and suggested an association of increased serum AFP with advanced fibrosis or cirrhosis.[26] In the present study Alpha feto protien was done to all the patients with a mean of 31±11.25 (SD) ng/dl and range of 1.3-55.3.A direct significant correlation was found between liver fibrosis stages and serum AFP. This was similar to the study of Chu et al.[27] (2001) who found that the severity of fibrosis/cirrhosis were significant predictors of elevated serum AFP. Also, Bayati et al.[28] in (1998) reported that elevated serum AFP was highly

specific for the diagnosis of cirrhosis among patients with chronic hepatitis C. In addition to this Hu et al.[26] (2004) found in a study that elevated serum AFP was strongly associated with stage III/IV fibrosis. From the above results it is shown that serum AFP levels reflect the degree of liver fibrosis. Because of this and because of the significant correlation that was found between liver fibrosis stages and HRCT score in patients of the present study, the relation between the AFP levels and HRCT score together with pulmonary function tests were investigated. A significant correlation was found between AFP levels and HRCT score otherwise there was no significant correlation among other parameters.

It was concluded that AFP levels also can be used for assessment of severity of interstitial pulmonary affection. This may need further studies in the future to investigate this conclusion.

It is known that viral load does not correlate with the severity of the hepatitis or with a poor prognosis (as it seems to in HIV infection); but viral load does correlate with the likelihood of a response to antiviral therapy (NIH Consensus Statement, 2002)[29]. However, in the present study there was significant inverse correlation between viremia level with DLCO% pred. There was no significant correlation between viremia level with HRCT, liver fibrosis, AFP, FEV1/ FVC, FVC% pred and /.FEV1%pred measurements. This may indicate that the level of HCV in the blood has direct effect on extrahepatic organs and that the more the level of the virus the greater its effect. Also, HCV induced activation of T-lymphocytes may play a pivotal role in the destruction of pulmonary parenchyma and antiviral treatment may block this activation (Yamaguchi et al., 1997). From the above studies it was found that there is an association between HCV infection and interstitial lung affection.

This idea put forth by investigators[5] from Japan who tested the presence of HCV antibodies in a group of patients with idiopathic pulmonary fibrosis (IPF); to their surprise, they found a higher prevalence of serum antibodies to HCV in patients with IPF (28.8%) than in age-matched control subjects (3.6%), which was statistically significant ($p < 0.05$). Although the findings of Irving[30] and his colleagues (1993) failed to confirm this linkage, more recent studies and case reports continue to point toward an association between chronic HCV infection and interstitial lung disease. Meliconi et al.[31] (1996) found a high incidence of HCV infection in Italian patients with IPF (13%), as well as an increased incidence of noninterstitial lung disease in HCV patients, suggesting that chronic HCV infection might affect the lungs through different mechanisms and lead to a spectrum of clinical presentations.

In summary, pulmonary involvement is one of the extrahepatic manifestations of chronic HCV infection. Despite a small study population, our findings support that HCV infection is related to the development of several pulmonary abnormalities despite the absence of symptoms. HRCT was better than pulmonary functions in assessment of these pulmonary alterations. The stage of liver fibrosis and the level of alpha-feto protein are important for anticipating the occurrence of interstitial pulmonary alterations.

Recommendations:

- Extending the same work on large number of cases.
- Further studies to investigate the relationship between alphafetoprotein, HCV viremia levels, liver fibrosis and pulmonary affection in HCV infected patients.
- Study the effect of interferon therapy on pulmonary function tests and HRCT of the chest.
- Prospective clinical studies are necessary to confirm the present observations as well as the actual prevelance of HCV infection in interstitial lung disease.

REFERENCES

1. Hoofnagle J. Hepatitis C: The clinical spectrum of disease. Hepatology. 1997;26:15S-20S.

2. Zignego AL, Ferri C, Monti M et al. Hepatitis C virus as a lymphotropic agent; evidences and pathogenetic implications. Clin Exp Rheumatol. 1995;13;33-7.

3. Ferri C, Greco F, Longombardo G et al. Hepatitis C virus antibodies in mixed cryoglobulinaemia patients.Arthritis Rheum. 1991;34:1606-10.

4. Moorman J, Fitzgerald S, Praythe r D B. Induction of p38- and gC1qR-dependent IL-8 expression in pulmonary fibroblasts by soluble hepatitis C core protein Respiratory Research. 2005;6:105.

5. Ueda T, Ohta K, Suzuki N, et al. Idiopathic pulmonary fibrosis and high prevalence of serum antibodies to hepatitis C virus. Am Rev Respir Dis. 1992;146:266-8.

6. Kuwano K, Nomoto Y, Kunitake R, Hagimoto N, Matsuba T, Nakanishi Y, Hara N. Detection of adenovirus E1A DNA in pulmonary fibrosis using nested polymerase chain reaction. Eur Respir J. 1997;10:1145-9.

7. Remy-Jardin M, Giraud F, Remy J, Wattinne L, Wallaert B, Duhamel A. Pulmonary sarcoidosis: Role of CT in the evaluation of disease activity and functional impairment and in prognosis assessment. Radiology. 1994;191:675-80.

8. French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. Hepatology. 1994;20:15-20.

9. Poynard T, Yuen MF, Ratziu V, Lai CL. Viral hepatitis C. Lancet. 2003;362:2095–100.

10. Saeed AA, Al-Admawi AM, Al-Rasheed A, Fairclough D, Bacchus R, Ring C, Garson J. Hepatitis C virus in Egyptian blood donors in Riyadh. Lancet. 1991;33:359–60.

11. Darwish NM et al. Hepatitis C virus infection in blood donors in Egypt. J Egypt Public Health Assoc. 1992;67:223–36.

12. Bassily S, Hyams KC, Fouad RA, Samaan MD, Hibbs RG. A high risk of hepatitis C infection among Egyptian blood donors: the role of parenteral drug abuse. Am J Trop Med Hyg. 1995;52:503–5.

13. Agnello V, De Rosa F. Extrahepatic disease manifestations of HCV infection: some current issues. J Hepatol. 2004;40:341–52.

14. Ferri C, La Civita L, Fazzi P, Solfanelli S, Lombardini F, Begliomini E, Monti M, Longombardo G, Pasero G, Zignego AL. Interstitial lung fibrosis and rheumatic disorders in patients with hepatitis C virus infection. Br J Rheumatol. 1997;36: 360-5.

15. Wittram C, Mark EJ, McLoud TC. CT-histologic correlation of the ATS/ERS 2002 classification of idiopathic interstitial pneumonias. Radiographics. 2003;23:1057–71.

16. Aziz Z, Wells A, Hansell D, Bain G, Copley S, Desai S, Ellis S, Gleeson F, Grubnic S, Nicholson A, et al. HRCT diagnosis of diffuse parenchymal lung disease: inter-observer variation. Thorax. 2004;59:506–11.

17. King T. Clinical Advances in the Diagnosis and Therapy of the Interstitial Lung DiseasesAmerican Journal of Respiratory and Critical Care Medicine. 2005;172:268-79.

18. Yamaguchi S, Kubo K, Fujimoto K, Honda T, Sekiguchi M, Sodeyama T. Analysis of bronchoalveolar lavage fluid in patients with chronic hepatitis C before and after treatment with interferon alpha. Thorax. 1997;52:33–7.

19. Rabie G. Evaluation of pulmonary functions in patients with chronic hepatitis C infection. MM.B.Ch, Cairo University. 2006.

20. Okutan O, Kartaloglu Z, Ilvan A, Kutlu A, Bozkanat E, Silit E (2004): Values of high-resolution computed tomography and pulmonary function tests in managements of patients with chronic hepatitis C virus infection.World J Gastroenterol February. 2004;1;10:381-4.

21. Erturk A, Tokgonul A, Capan N, Erturk H, Dursun A, Bozkaya H. Pulmonary alterations in patients with chronic HCV infection. Digestive and Liver Disease. 2006;38:673–6.

22. Manganelli P, Salaffi F, Subiaco S, Carotti M, Cevrini C, Consigli G, et al. Bronchoalveolar lavage in mixed cryoglobulinaemia associated with hepatitis C virus. Br J Rheumatol. 1996;35:978–82.

23. Salaffi F, Manganelli P, Carotti M, Subiaco S, Cervini C. Mixed cryoglobulinemia: effect of alpha-interferon on subclinical lymphocyte alveolitis. Clin Exp Rheumatol. 1996;14:219–317.

24. Fernando J, Flaherty K. Pulmonary Function Testing in Idiopathic Interstitial Pneumonias. The American Thoracic Society. 2006;3:315-21.

25. Hoofnagle J. Hepatitis C: The clinical spectrum of disease. Hepatology. 1997;26:15S-20S.

26. Hu KQ, Kyulo NL, Lim N, Elhazin B, Hillebrand DJ, Bock T. Clinical significance of elevated alpha-fetoprotein (AFP) in patients with chronic hepatitis C, but not hepatocellular carcinoma. Am J Gastroenterol. 2004;99:860-5.

27. Chu CW, Hwang SJ, Luo JC, Lai CR, Tsay SH, Li CP, Wu JC, et al. Clinical, virologic, and pathologic significance of elevated serum alpha-fetoprotein levels in patients with chronic hepatitis C. J Clin Gastroenterol. 2001;32:240-4.

28. Bayati N, Silverman AL, Gordon SC. Serum alpha-fetoprotein levels and liver histology in patients with chronic hepatitis C. Am J Gastroenterol. 1998;93:2452-6.

29. National Institutes of Health Consensus Conference Statement (NIH). Management of Hepatitis C.Hepatology. 2002;19:1-46.

30. Irving WL, Day S, Johnston ID. Idiopathic pulmonary fibrosis and hepatitis C virus infection. Am Rev Respir Dis. 1993;148:1683-4.

31. Meliconi R, Andreone P, Fasano L, et al. Incidence of hepatitis C virus infection in Italian patients with idiopathic pulmonary fibrosis. Thorax. 1996;51:315-17.