Original Article

Frequency of Pulmonary Fibrosis in Patients with Cirrhosis of Liver

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Background: Cirrhosis of liver and pulmonary fibrosis both are chronic inflammatory disorders. Mediators of chronic inflammation include both cytokines and interleukins. The mediators produced during process of fibrosis in liver reach pulmonary circulation which comes first during the pathway; so these mediators should lead to fibrosis in lungs as well.
Material and Methods: 55 patients of age range 16 to 80 year, both males and females having established cirrhosis of liver on ultrasonography, regardless of etiology, visiting the outpatient and inpatient departments for treatment of liver disease were selected. High Resolution Computerized Tomography (HRCT) Scan of chest was performed on each patient to look for pulmonary fibrosis.
Results: Out of 55 patients 27 (49%) were found to have pulmonary fibrosis on HRCT.
Conclusion: Cirrhosis of liver is associated with pulmonary fibrosis in up to 50% of the patients.
Key Words: Cirrhosis, Pulmonary fibrosis, High resolution CT scan.

Introduction

Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen, that occur in most types of chronic liver disease. Advanced liver fibrosis results in cirrhosis, liver failure and portal hypertension and often requires liver transplantation.[1,2] It is now recognized that hepatic stellate cells, portal fibroblasts and myofibroblasts of bone marrow origin are primarily responsible for hepatic fibrosis and subsequent progression to cirrhosis.[3] These cells are activated by fibrogenic cytokines such as transforming growth factor beta (TGF), angiotensin II and leptin as well as proliferative cytokines like platelet derived growth factor.[1,2,3] It has been shown that locally synthesized angiotensin II is also a fibrogenic factor (PDGF) and is involved in pathogenesis of cardiac fibrosis, renal interstitial fibrosis as well as pulmonary fibrosis.[4,5,6]

In Pakistan, the most common cause of chronic liver disease is viral hepatitis. In one study conducted at Mayo Hospital, Lahore, 68% of patients were positive for anti HCV antibody, 23% for HBsAg and 9% for both.[7]

Non-hepatological manifestations are frequent, with more than 70% of HCV patients experiencing fatigue or at least one extra hepatic clinical manifestation involving primarily the joints, skin or muscles. Several immunological abnormalities are frequently observed, including cryoglobulins, anti-nuclear antibodies and anti-smooth muscle antibodies. In contrast, severe extra hepatic manifestations are rare, with 1% for systemic vasculitis as an exception.[8]

Objectives

The study was conducted to determine the frequency of pulmonary fibrosis in patients with cirrhosis of liver.

Material and Methods

This study was conducted at Medical Unit-IV of Services Hospital, Lahore. Total study period was six months, starting from November 2003 till April 2004 & a total of 55 patients were recruited.

Inclusion Criteria

Patients between 16 to 80 years of age presenting to medical outpatient department or admitted to Medical Unit-IV having established cirrhosis of liver on the basis of ultrasonography regardless of etiology were included in study.

Exclusion Criteria

1. Patients with pulmonary tuberculosis.
2. Patients with primary lung tumor or lung metastasis.
3. Patients with sarcoidosis.
4. Patients with history suggestive of autoimmune disorders.
5. Patients with history of exposure to asbestos.
6. Patients on interferon or chemotherapy.
7. Patients with history suggestive of chronic obstructive air way disease.

Data Collection Procedure

1. Patients were recruited according to inclusion criteria.
2. Ultrasonography was done on every patient (for coarse echotexture, reduced liver span in mid clavicular line, portal vein dilatation in cm, splenic size in cm and presence or absence of ascites).
3. HRCT was done on every patient to demonstrate the presence or absence of pulmonary fibrosis.
4. The HRCT films were reported by the same radiologist.

Results

This study included 55 patients. Patients of both sexes were included in the study. Out of 55 patients 30 (55%) were males and 25 (45%) were females. Age distribution is shown in **Table 1.**

HRCT scan of lungs was performed on all 55 patients. 27 patients (49%) showed evidence of pulmonary fibrosis while 28 patients (51%) did not show any evidence of pulmonary fibrosis **(Table 2)**. Out of 27 patients who had pulmonary fibrosis 15 patients (55%) were male while 12 patients (45%) were female **(Table 3)**.

Table-1: Age distribution in years.

Age in years	Frequency	Percentage
15 - 25	01	03.0
26 - 35	03	06.0
36 - 45	16	27.0
46 - 55	19	32.0
56 - 65	12	22.0
66 - 75	03	07.0
> - 75	01	03.0

Age range 16 80 years
Minimum age = 16 years
Maximum age = 80 years
Mean ± SD 29.79±5.30

Table 2: Pulmonary Fibrosis on HRCT.

HRCT	No. of patients	Percentage
Positive	27	49.0
Negative	28	51.0

Table-3: Pulmonary Fibrosis in Cirrhosis Sex- wise.

Sex	No. of patients	Percentage
Male	15	55.0
Female	12	45.0

Discussion

Viral hepatitis is the major cause of cirrhosis in Pakistan. Prevalence of hepatitis C is more than hepatitis B.[9] In western world, alcoholic liver disease accounts for 60-70% cases of cirrhosis. Other causes of cirrhosis include cryptogenic cirrhosis (10-15%), biliary disease (5-10%), genetic haemochromatosis (5%), Wilson's disease and alpha-1 anti-trypsin deficiency.

Incirrhosis, there is increased deposition of collagen (type I and II) and stimuli for deposition of collagen come from cytokines produced by chronic inflammation, like TNF alpha and beta, interleukin-1 (IL-1) by injured endogenous cells.[10]

The frequency of interstitial lung disease in chronic liver disease of different etiologies varies between 13 to 60% in the literature published. This study shows that frequency of pulmonary fibrosis in patients with cirrhosis of liver is much more i.e. 49% as compared to frequency in general population (3% in Western population).

Interstitial lung disease appears medially 4.5±3.2S.D years after clinical onset of chronic hepatitis. Abnormalities in pulmonary function have been reported in association with chronic liver disease of varied etiology e.g. in one study most commonly affected test of lung function was reduced lung capacity for carbon mono-oxide (DLCO), followed by ventilatory restriction (25%) and air flow obstruction (3%).[9] Pulmonary function is further impaired in cirrhosis and ascites causes further deterioration.[10] In another study obstructive airway disease was found in 11%, restrictive lung disease in 17% and reduced diffusion capacity in 43%.[11]

Patients with primary biliary cirrhosis develop interstitial lung disease with moderately restrictive lung function tests. Also idiopathic pulmonary fibrosis is associated with cirrhosis due to hepatitis C virus. [12,13] These studies also favor the results of this study as most of patients here suffering from chronic hepatitis C were found to have co-existing pulmonary fibrosis.

Another study conducted in Japan in 1992 showed high prevalence of anti HCV antibodies (28.8%) in patients with idiopathic pulmonary fibrosis.[13] It means that HCV may be a contributing factor in

development of pulmonary fibrosis. This study also favors the results of our study as most of patients in this series suffering from chronic hepatitis C were found to have co-existing pulmonary fibrosis. Subsequent British study in 1993 showed that HCV infection is no more prevalent in patients with IPF as compared to general population.[14] This is in contrast to the results of our study.

In 1996 an Italian study showed that prevalence of anti HCV antibody in IPF is 13%[15] which again shows that there might be a relationship between these two entities. We hypothesized that the mediators of chronic inflammation produced during the process of liver fibrosis like transforming growth factor beta (TGF-β) as well as platelet derived growth factor (PDGF), reach the right heart and then the pulmonary circulation, so should lead to fibrosis of lungs.

Knowledge of cellular and molecular mechanisms of cirrhosis (liver fibrosis) has greatly advanced. The cytokines involved in fibrosis of liver stimulate the collagen producing cells in the injured liver. Reversibility of advanced liver fibrosis has been recently documented. This has stimulated the researchers to develop new anti-fibrotic drugs and a lot of work is being done to treat fibrosis in liver. Research in future could focus to determine the correlation between cirrhosis and pulmonary fibrosis. Tissue cultures and biopsies of both lung parenchyma and liver can be helpful in assessing this relationship.

Treatment of liver disease with drugs like interferon will possibly reduce the severity of fibrosis in lungs also. In fact, both diseases could be treated with similar drugs.

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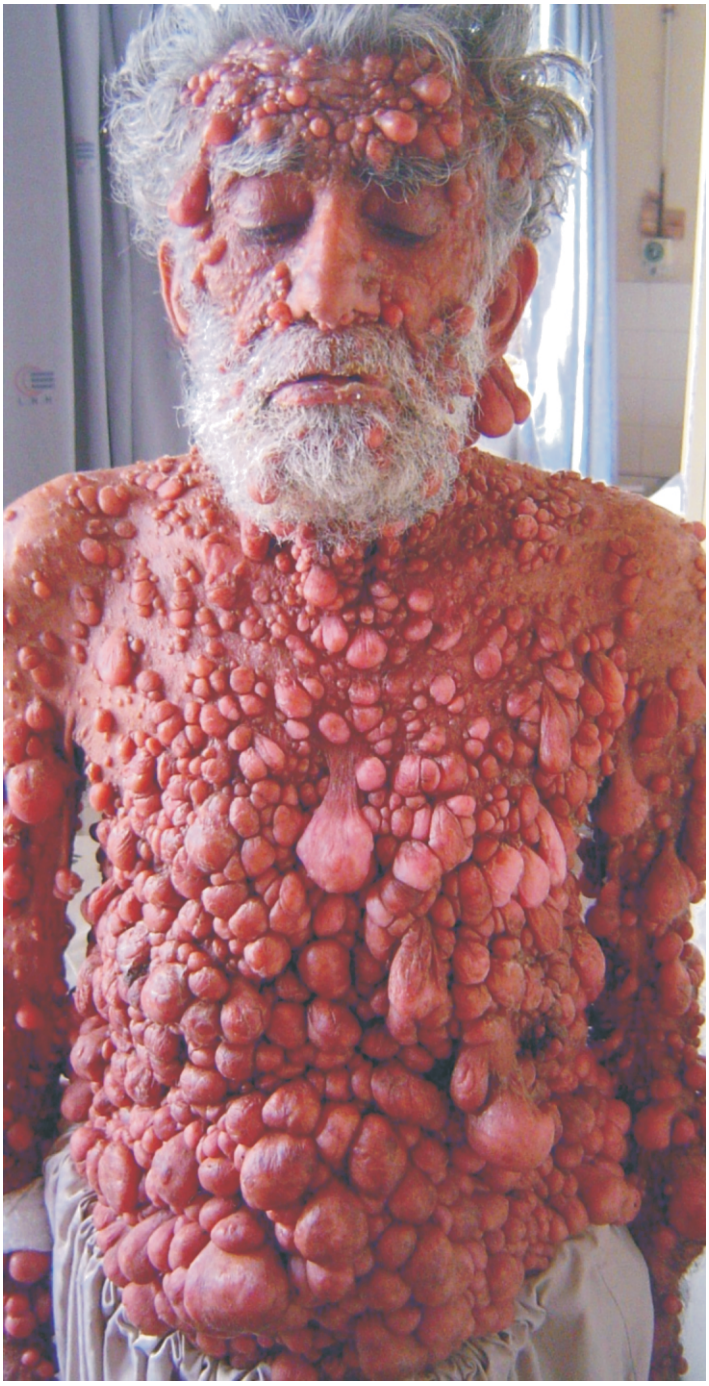
Picture Quiz

A 70-year-old man had generalized slowly progressive growths without neurologic complications. One of his daughters was also affected.



1.What is the diagnosis?

2.What is the etiology of this condition?

3.What neurological complications can possibly occur?

4.What is the treatment?

5.What is the role of counseling?

Answer of Picture Quiz on page number 31