ABSTRACT

Background: Cirrhosis can cause various cardiac complications and severely affect the prognosis of the patient suffering from cirrhosis. Anatomical, morphological variations in the heart of patients with liver cirrhosis in the absence of known cardiac disease has not been well described. There is a paucity of studies in the literature on cardiac alterations in cirrhosis. Early detection of known cardiac alterations can further help in improving the quality of life.

Materials and Methods: A cross-sectional descriptive study was conducted in the departments of pathology and forensic medicine of our institution. An autopsy-based prospective study of forty consecutive patients with final diagnosis of liver cirrhosis were included. Patients with a known history of cardiac disease/anomaly were excluded from the study. Macroscopic and microscopic changes in the heart and coronaries were noted and statistically analyzed.

Results: Analysis of the hearts on gross examination showed cardiomegaly in 31 patients (77.5%). All cases had left ventricular hypertrophy. Endocardial thickening was seen in 22 patients (55%). Calcified mitral valve was seen in 9 patients (22.5%). On microscopy, apart from hypertrophy, the pathological changes like interstitial oedema (47.5%), fibrosis (45%), cardiac muscle disarray (87.5%), fatty infiltrate (10%), pericarditis (5%), and severe coronary artery atherosclerosis (17.5%) were seen in the patients.

Conclusion: Knowledge about the involvement of the heart in liver cirrhosis is essential for both the physician and the surgeons to prevent adverse outcomes during liver transplantation and can further help in improving the quality of life of the patient.

Key words: Cardiomyopathy, cirrhosis, fibrosis, ventricular hypertrophy

INTRODUCTION

Liver cirrhosis (LC) is a fatal condition with well-recognized cardiovascular complications. The cardiac pathology mainly includes cirrhotic cardiomyopathy (CCm), hepatopulmonary syndrome, and porto-pulmonary hypertension.

INTRODUCTION
these alterations can also occur in patients with non-
alcoholic liver cirrhosis. Kowalski, et al (1953) were the first to report an increase in resting cardiac output and decreased systemic vascular resistance and a prolonged QT-interval in patients with cirrhosis.

Cardiac impairment secondary to liver cirrhosis or heart diseases complicated by liver dysfunctions are designated under a group of disorders called hepatocardiomyopathy syndromes. The heart, blood vessels, and the liver are interconnected through hemodynamic mechanisms related to the sympathetic system. Cirrhosis is often associated with hemodynamic changes like portal hypertension, vascular resistance, splanchnic vasodilation, bleeding due to extra hepatic manifestation, cardiac changes, and hyper-dynamic circulation. Different pathophysiological mechanisms including neurogenic, humoral, and vascular dysregulations are implicated in the pathogenesis of these cardiovascular changes. This relationship between hepatic and cardiac disorders should prompt the evaluation of the functional state of the heart and the liver before the adequate management of concerned patients with both organ dysfunction.

Initially, research revealed a low prevalence of atherosclerosis in patients with cirrhosis and concluded that cirrhosis of the liver had a protective role for coronary artery disease (CAD). However, recent studies have revealed a high prevalence of asymptomatic CAD in these patients. At the same time, the prevalence of the coronary artery calcification is also high which is considered as an independent predictor of cardiovascular risk.

The anatomical and electro-physiological variations in the heart of patients with LC in the absence of known cardiac disease is well established. There are very few autopsy studies in the literature that have described the histological cardiac changes like subendocardial and myocardial edema, patchy fibrosis, and myocardial hypertrophy.

MATERIALS AND METHODS

The study was conducted in the Department of Pathology. We included all the autopsy specimens received from Forensic Medicine Department of our institution. All the patients with a final diagnosis of LC on autopsy were included. Patients with a known case of cardiac disease/anomaly were excluded from this study. The diagnosis of LC was established according to the criteria of the World Health Organization (WHO), that is, parenchymal necrosis, regeneration, and diffuse fibrosis, resulting in disorganization of the lobular architecture throughout the whole of the liver. The data were retrieved from medical history records. The heart specimens were perfused by the coronary perfusion method, using 10% buffered formalin.

The heart was weighed and dissected by the inflow–outflow technique. First, superior vena cava up to inferior vena cava was opened. Valves were cut between their commissures. Then, the right ventricle inflow tract to the right apex and right outflow tract to pulmonary arteries was opened. The left atrium extending into the appendage was opened. Later, dissection of the left ventricular inflow tract to the left apex and left outflow tract along pulmonary artery, cutting through the left coronary artery was done.

Short-axis method was used in case of sudden death. The four-chamber cut method was used the case of cardiomyopathy. Cavities, valves, papillary muscles, and chordae tendineae were inspected. Cross sections across the coronary arteries of 3 mm intervals starting close to the aorta were taken and examined. Heart wall thickness and valvular circumferences were measured.

Cardiomegaly was established when heart weight was >300 g, left ventricular hypertrophy (LVH) when the average thickness of left ventricle was higher than 1 cm, right ventricular hypertrophy when the average thickness of the right ventricle was >0.3 cm, and valvular heart disease when the valve diameter (measured at the valvular ring) or its morphology was altered.

The anterior and posterior walls of the left ventricle with papillary muscles, septum, right ventricular outflow tract, areas with macroscopic abnormalities, and coronary arteries were sampled; sections were processed and stained by hematoxylin and eosin stain (H and E). On light, microscopic examination, all the changes were noted. A special stain like Masson's trichrome was used to highlight collagen in interstitial and patchy fibrosis. Macroscopic and microscopic changes in the heart and coronaries were statistically analyzed.

RESULTS

Autopsy specimen of hearts belonging to the patients who expired due to cirrhosis of the liver were taken up for evaluation. There were forty patients aged between 25 - 75 years, thirty-nine were male, and only one was female patient. On gross examination of the hearts, cardiomegaly was seen in 31 patients (77.5%) [Figure 1a]. The measurements of ventricular muscle thickness and weight of the heart are tabulated in Table 1. All the patients had LVH. Biventricular hypertrophy was seen in 37 patients (92.5%). Interventricular septal hypertrophy was seen in 28 patients (70%) [Figure 1b]. Endocardial thickening was seen in 22 patients (55%). The calcified mitral valve was seen in 9 patients (22.5%) and left ventricular papillary muscle hypertrophy was seen in 20 patients (50%). Left ventricular chamber size was reduced in 9 patients (22.5%) compared to right ventricular chamber size. Both right and left ventricu
chamber size were reduced in two patients (5%). Both the chambers were dilated in one patient (2.5%). The gross findings of all the patients are represented in Table 2.

On microscopic examination, left ventricular hypertrophy was confirmed in all the cases. The frequency of microscopic findings such as fatty infiltrates [Figures 2a and b], interstitial cardiac oedema [Figure 3a], interstitial as well as patchy fibrosis [Figure 3b], and muscle disarray are represented in Table 3. In patients with fatty infiltrate in myocardium, moderate to severe coronary artery disease in the form of atherosclerotic change was observed. All three patients with patchy fibrosis of ventricles had severe coronary artery disease.

Mitral valve annular calcification was seen in nine patients (22.5%) and only one of the patients had aortic valve calcification along with mitral valve calcification.

Mild to severe atherosclerotic changes were seen in coronaries. The most commonly involved vessel was the left coronary artery branch, the left anterior descending artery, followed by the right coronary artery. Out of twenty-five patients with coronary artery atherosclerosis, nine had right coronary artery involvement. The left anterior descending artery also showed near complete occlusion of the lumen by atherosclerosis [Figure 4a-c]. The severity of coronary artery atherosclerosis is represented in Table 4.

The other gross findings which was noted was dilated cardiomyopathy in two patients (5%) and banana-shaped interventricular septum in one patient (2.5%). Microscopically, acute myocarditis was seen in four patients (10%). One of the patients showed a large area of inflammation with infarct and fibrosis.

DISCUSSION

The involvement of the cardiovascular system in end-stage liver disease is well recognized, and there are reports of cardiovascular symptoms in patients with liver cirrhosis including arrhythmias, chronotropic incompetence, cardiomyopathy, prolonged QT intervals, hyperdynamic circulation with an increased cardiac output and decreased peripheral vascular resistance, and impaired ventricular contractility in response to of physiologic and pharmacologic stimuli. However, there are very few autopsy and ultrastructural studies illustrating the morphological changes in the heart.[41]
The pathological features like left ventricular dilatation, myocyte loss, interstitial fibrosis with myofibrillar disruption leading to myocyte hypertrophy, and increase in left ventricular mass of LC patients could be due to ultrastructural injury caused by heavy alcohol consumption. The ultrastructural changes consistently seen are intracellular organelle dysfunction or protein alterations.[17]

The histological cardiac changes in cirrhotic cardiomyopathy is described five decades ago and subsequently confirmed in many studies. These early histological studies have described myocardial hypertrophy, especially LVH, ultrastructural changes such as cardiomyocyte edema, fibrosis, exudation, nuclear vacuolation, and unusual pigmentation.[18-20]

The pathogenesis of cardiac changes in LC is not well established, even though many mechanisms such as physiological alterations with autonomic cardiovascular dysfunction and biochemical modifications involving endocannabinoids, nitric oxide, and carbon monoxide have been postulated. The impaired cardiovascular responsiveness in cirrhosis may be related to a combination of factors that include cardiomyocyte plasma membrane physicochemical changes, attenuated stimulatory pathways, and enhanced activity of inhibitory systems.[6,8,15]

In a study done by Torregrosa et al., it was found that the cardiac changes in cirrhosis are independent of the etiology of cirrhosis. Lunzer et al. in their study found that cardiac dysfunction in cirrhotics did not correlate with the etiology of cirrhosis. In our study, cardia in cirrhosis was analyzed irrespective of its etiology. It showed morphological, microscopic changes in the heart and coronary arteries.[21,22]

Vaideeswar et al. studied the cardiac changes in the cirrhotic group and showed increase in ventricular thickness in comparison to non-cirrhotic group, similar to our study. In the same study, interstitial fibrosis (100%), myocyte degeneration (61.5%), inflammation (53.8%), and intramyocardial fat (23.1%) were seen though of higher percentage when compared to the present study. However, the sample size is small - only thirteen patients were studied by Vaideeswar et al.

Significant coronary artery atherosclerosis was noted in 17.5% of patients in this study which is higher than the Vaideeswar et al. study (7%).[23] Cardiomegaly and ventricular hypertrophy were the most common anatomic abnormalities in Ortiz-Olvera et al. study. They have further confirmed that myocardial alterations are common in patients with cirrhosis and that its development is mainly related to the degree of liver failure, rather than the cirrhosis etiology.[14]

In recent studies, alcohol is known to exert adverse cardiovascular effects such as macro- and microvascular dysfunction, increased atherosclerotic plaque development, and coronary calcification when actually low serum cholesterol, low blood
pressure values, and higher levels of circulating estrogens in cirrhosis should protect against coronary atherosclerosis.[24-27]

In the present study, the atherosclerotic plaque was seen in all patients and coronary calcification was seen in four patients (10%). Experimental animal mouse models and autopsy studies have confirmed the association of alcoholic cardiomyopathy with cardiac steatosis. Cardiac steatosis can lead to the development of cardiac dysfunction in turn leading to dilated cardiomyopathy.[28,29] Studies have shown that fatty infiltration of ventricles, especially perivascular accelerates aortic atherosclerosis and is confirmed in our study as well.[30] Myocardial hypertrophy, especially LVH and increased interventricular septum with fibrosis cause diastolic dysfunction and contribute to structural heterogeneity and risk of arrhythmia.[31]

Autopsy studies have described subendocardial and myocyte oedema and patchy fibrosis, in addition to myocardial hypertrophy.[11] In the present study, 70% of patients had interventricular septal hypertrophy and 47.5% had myocyte oedema. In view of high frequency of CCm and CAD, a careful cardiac evaluation of patients with LC is required before liver transplantation.

CONCLUSION

Liver cirrhosis is a fatal condition which usually causes many systemic manifestations, especially in the heart and coronaries which leads to both morphological and microscopical changes. In our study, the relation between the heart and the liver in LC has been established. Knowledge about the involvement of the heart in LC is essential for both the physician and the surgeons to prevent adverse outcomes during transplantation and can further help in improving the quality of life of the patient.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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