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# Cirrhotic Cardiomyopathy in Maternal Death – A Case Report and Review of Literature

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**Abstract:** ***Cirrhotic cardiomyopathy (CCM) is the term used to describe a constellation of features indicative of abnormal heart structure and function in patients with cirrhosis. These include systolic and diastolic dysfunction, electrophysiological changes, macroscopic and microscopic structural changes. The disease is generally latent. Major stresses on the cardiovascular system such as infections, surgery etc can unmask the presence of cirrhotic cardiomyopathy and thereby convert latent to overt heart failure. Pregnancy and delivery were the precipitating factors in case of 20 years primigravida. Clinical and autopsy findings proved that she was suffering with cirrhotic cardiomyopathy.***

**Keywords:** Cirrhotic cardiomyopathy, stresses, autopsy

## 1. Introduction

There are main three types of cardiomyopathy i.e. dilated, restrictive and hypertrophic cardiomyopathy. Here we report a very unusual, underdiagnosed, under-reported case of cardiomyopathy that is Cirrhotic cardiomyopathy. Cirrhosis is very common in India. Cardiac hypertrophy and cardiomyocyte edema in the absence of coronary artery disease, hypertension, or valvular disease were next described in an autopsy series of subjects with cirrhosis [1]. Subsequent studies described an impaired hemodynamic response to physiologic (exercise) and pharmacologic stress despite a high resting cardiac output [2]. CCM is a diagnosis of exclusion and other causes of cardiac dysfunction including valvular heart disease, congenital heart disease, ischemic heart disease, conduction abnormalities, and hypertrophic cardiomyopathy should be excluded [3-4].

The epidemiology and natural history of CCM is not well defined. The onset is insidious, latency time is long, and it is often undiagnosed, or a diagnosis is made late in the course of the disease [5-8].

## 2. Results

A 20 years old primigravida, delivered normally at term at primary health care centre where very limited investigation facilities were available. Soon after delivery she had generalised tonic clonic convulsions followed by which she became unconscious. She was brought in an unconscious state in our hospital. The total stay in our hospital was one day.

Electrocardiogram showed prolongation of QT interval. The other investigations like 2D Echo, Stress test, coronary angiography etc were not possible. Relatives gave the history of full term normal delivery and about live birth baby. Relatives also gave history of loss of appetite, breathlessness, palpitations and fatiguability since 6 months and history of pedal oedema since 2 months. She succumbed to death even after using all resuscitative measures. To find out exact cause of death, autopsy was performed by a team of forensic expert, pathologist and gynaecologist. Pallor and pedal oedema were the only findings on external examination during autopsy. Internal examination showed all organs in their normal anatomical positions.

## 3. Gross and Microscopy

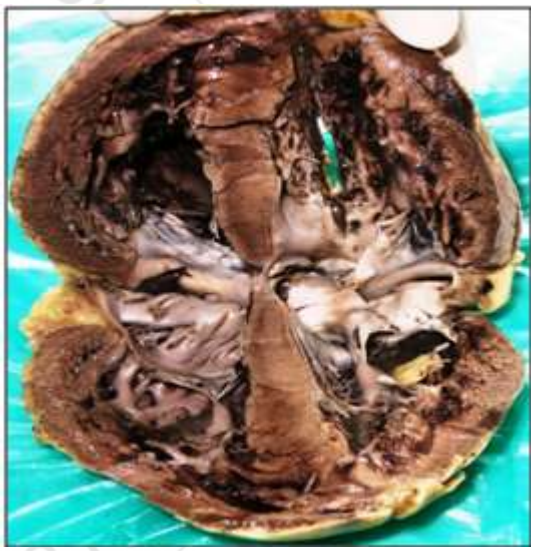

**Figure 1:** Shows dilatation of all chambers of the heart

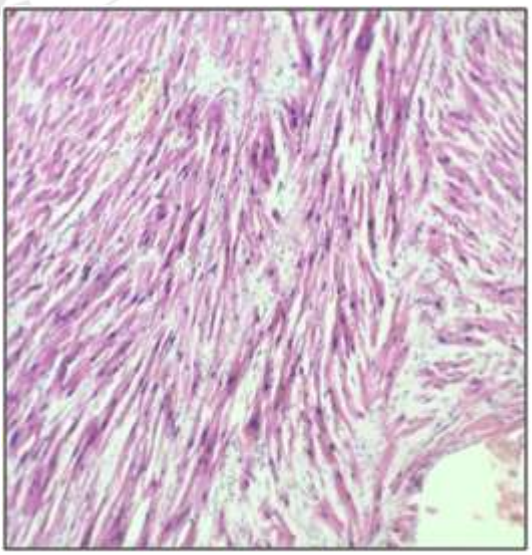

**Figure 2:** Shows disarray and hypertrophy of myocytes with Collagenisation

**Figure 3:** Shows diffusely scattered micro and macronodules on external and cut surface of liver

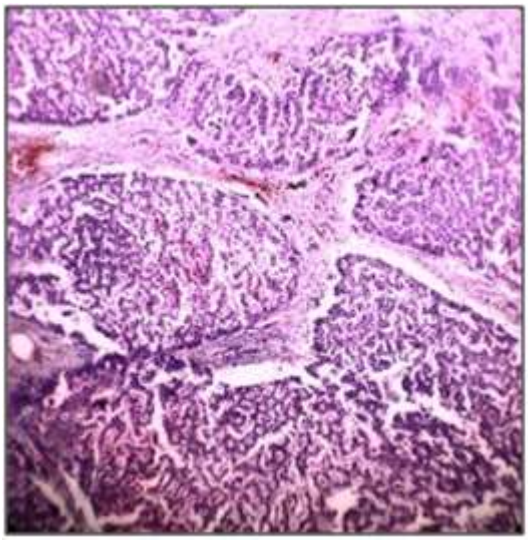

**Figure 4:** Shows pseudolobule formation with loss of normal liver architecture

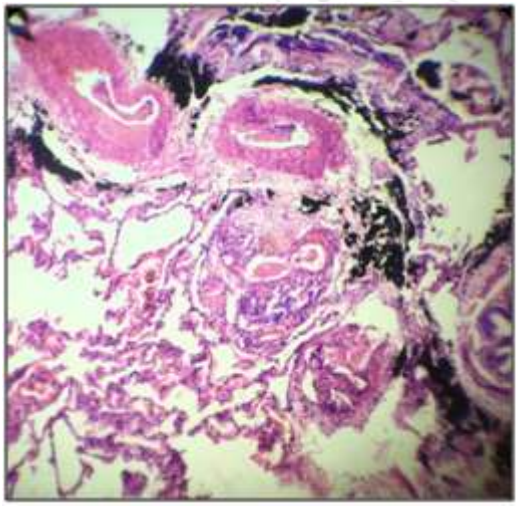

**Figure 5:** Shows hypertrophy of pulmonary vessels and plexogenic pulmonary arteriopathy

## 4. Discussion

Cirrhotic cardiomyopathy (CCM) is a clinical syndrome in patients with liver cirrhosis characterized by an abnormal and blunted response in cardiac output and contractility to physiologic, pathologic, or pharmacologic stress but a normal to increased cardiac response at rest [5, 6, 7, 8]. Without firm diagnostic criteria, the exact prevalence of cirrhotic cardiomyopathy remains unknown. Its estimation is a difficult task as the disease is generally latent and shows itself only when the patient is subjected to stress such as body position changes, exercise, drugs, hemorrhage and surgery. The prevalence of liver cirrhosis is also difficult to estimate, because many persons with compensated cirrhosis do not exhibit signs or symptoms of the disease and because noninvasive studies lack sensitivity to detect cirrhosis at early stages. Moreover there is tremendous geographical variability of cirrhosis worldwide, depending on the prevalence of the causative factors such as viral hepatitis B and C, chronic alcoholism, iron overload, autoimmune liver disease, etc [7].

## 5. Pathogenetic mechanisms underlying cirrhotic cardiomyopathy

### 5.1 Systolic dysfunction

Cardiomyocyte contractility is mainly regulated by b-adrenergic stimulation. The binding of either adrenaline or noradrenaline on to the b-adrenergic receptor leads to the interaction of the receptor with a binding protein known as the Gs or the stimulatory protein. This, in turn, leads to the activation of another membrane-bound protein known as adenylate cyclase. The net result is the production of cAMP from adenosine triphosphate (ATP). The Gs protein also promotes the direct activation of the calcium channel of the sarcolemma. Cyclic AMP plays a crucial role in activating protein kinases; one of these is protein kinase A, which phosphorylates several proteins including the calcium release receptor located within the sarcoplasmic reticulum. This promotes the influx of calcium into the cytosol of the cardiomyocyte, causing actin-myosin myofibrillar cross-linking, which results in cellular contraction (Figure 6)[9].

In cirrhosis, several abnormalities in the b-adrenergic signaling pathway have been identified. For example, there is a decrease in b-adrenergic receptor density, a reduction in Gs proteins, and attenuation of adenylate cyclase activity with resultant decreased cAMP generation [10], all of which negatively affect cardiomyocyte contractility. In addition, there have been reports of altered membrane fluidity due to changes in the lipid composition of the cardiomyocyte plasma membrane [11, 12]

In chronic liver disease, there is significant upregulation of the cannabinoid signalling pathway [13]. In the cardiomyocyte, cannabinoids subtype-1 (CB-1) receptors are known to exert a negative inotropic effect via activation of the inhibitory G (Gi) protein. The Gi protein inhibits adenylate cyclase activity, reducing the production of cAMP with resultant decreased calcium influx into the cytosol of the cardiomyocyte (Figure 6)[14].

The NO and carbon monoxide (CO) pathways also have a negative effect on cardiomyocyte contraction. Both NO and CO are evanescent gases produced in the cirrhotic heart by increased inducible NO synthase and hemoxygenase

activities, respectively. Both gases stimulate guanylate cyclase to produce cyclic guanosine monophosphates (cGMP), which phosphorylates protein kinase G to inhibit calcium influx into the cytosol of the cardiomyocyte (Figure 6). Stimulation of the NO pathway is possibly related to increased cytokines in cirrhosis, as significantly increased tumor necrosis factor-a (TNF-a) and cGMP contents have been reported in bile duct ligation model of cirrhotic rats [15].

Systolic dysfunction may also contribute to sodium retention in cirrhosis. Decrease in cardiac contractile function is consistently associated with sympathetic activation, both in early and advanced cirrhosis [16]. Increased baroreceptor- and volume-receptor-mediated sympathetic firing with subsequent neuronal release of norepinephrine is a physiological response to increase cardiac contractility, thereby returning cardiac performance to an adequate level but at the cost of substantial encroachment on the Frank-Starling reserve [17]. But this sympathetic overdrive can also directly stimulate renal sodium and water retention and indirectly activate the renal RAS, which enhances the renal sodium and water retention [18].

**5.2 Diastolic dysfunction**

The presence of diastolic dysfunction leads to abnormal left ventricular relaxation during diastole, usually owing to decreased dispensability of cardiac tissue, the result of either hypertrophy of cardiomyocytes or increased interstitial collagen deposition. Therefore, there is impedance to ventricular inflow, and the end-diastolic left ventricular pressure is elevated relative to the left ventricular end-diastolic volume [1]. There is no direct evidence from either human or animal studies that explore the pathogenesis of diastolic dysfunction in cirrhosis. Increasing the sodium intake has been shown to increase their left ventricular weight by 20–25% without increasing their resting blood pressure, cardiac filling pressure, or cardiac sympathetic activity [19, 20, 21], suggesting that excess sodium per se can induce myocardial hypertrophy independent of volume expansion. Alternatively, it has been suggested that high sodium intake stimulates the intracardiac production of various cytokines, including transforming growth factor (TGF)-b. TGF-b in turn, acts in an autocrine or paracrine fashion to increase the production of endothelin 1 [22], which also has direct trophic effects on the myocardium [23].

**5.3 Electrophysiological abnormalities**

Electrophysiological abnormalities in cirrhosis are due to a combination of plasma membrane changes, b-adrenoceptor and postreceptor pathway defects, and a generalized ion channel dysfunction [24]. All of the aforementioned abnormalities in membrane fluidity and b-adrenergic signalling pathway in cirrhosis can lead to a delay in the electrical excitation and its mediation of the mechanical contraction, resulting in impaired electromechanical coupling.

Various ion channel defects in cirrhosis have now been associated with prolongation of the action potential of the cardiomyocytes, which results in extension of ventricular systole or a prolonged QT interval. With adrenergic stimulation, rapid depolarization occurs as a result of opening of sodium (Na+) channels, leading to a rapid influx of Na+ into cardiomyocytes. At a slightly higher voltage, the slow calcium (Ca2+) channels open, allowing Ca2+ to enter the cardiomyocytes. This initiates myocardial contraction. The Na+ channels then close and Na+ Flux ceases. Outward rectifier potassium (K+) channels then open transiently, extruding K+ while Ca2+ influx continues. The Ca2+ channels then close, whereas K+ efflux continues through the delayed rectifier K+ channels, and repolarization occurs. Finally, the K+ channels close, and Na+ and Ca2+ are being actively pumped out to return to the resting state. Impaired function of K+ channels in cirrhosis has been reported [25], thereby reducing K+ extrusion and prolonging the action potential or the QT interval.

"Cirrhotic cardiomyopathy" is defined at present as: 1) baseline increased cardiac output but blunted ventricular response to stimuli, 2) systolic and/or diastolic dysfunction, 3) absence of overt left ventricular failure at rest, 4) electro-physiological abnormalities including prolonged QT interval on electrocardiography and chronotropic incompetence [26, 27, 28, 29]. Cirrhotic cardiomyopathy is characterised by abnormal heart structure and function in patients with cirrhosis [7].

CCM is diagnosed based on electrocardiographic and echocardiographic criteria [30]. Electrocardiographic abnormalities in CCM include QT prolongation (corrected QT interval > 0.44 s) or multiple extrasystoles due to hyperdynamic state, as well as bundle branch block and electromechanical dyssynergy during acute decompensation and hypotension [5, 18, 30, 31, 32, 33, 34].

Echocardiographic features of CCM include prolonged isovolumic time (>80 msec), E/A ratio ≤ 1, and decreased pattern of contractility with preserved systolic function (LVEF > 50%) during the hyperdynamic state, as well as decreased wall motion, increased wall thick- ness and enlarged atrium during acute decompensation and hypotension [5, 18, 30, 31, ].

In most studies of patients with cirrhosis, the heart mass has been found to be within the normal range [35, 36]. However, some have reported an increased left ventricular mass [18, 37] and in experimental study of portal hypertensive rats, left eccentric hypertrophy was found to correlate directly with the degree of hyperdynamic circulation [38]. In echocardiographic studies, Kelbaek *et al* [39] and Rector *et al* [40] found the size of the left ventricle to be normal and that of the left atrium enlarged [41, 42]. The size of the left atrium and ventricle in patients with cirrhosis is normal to increased. No definite conclusion can be offered as to the size of the right heart [28]. In our case, all chambers of the heart were dilated.

On autopsy examination after opening the chest, significant portion of the heart was not covered with lung, as the heart was dilated. The whole heart weighed 350gms. All coronaries and aorta were unremarkable (Figure 1). Liver

weighed 900gms. It's external and cut surface showed diffusely scattered micro and macronodules (Figure 2). Microscopically right atrium, right and left ventricles, apex, interventricular septum and papillary muscle showed hypertrophy of the myocytes with enlarged nuclei, attenuation, increased inter-myocyte collagen and disarray (Figure 3). These findings suggest dilated cardiomyopathy. Liver showed pseudolobule formation with loss of normal architecture (Figure 4). Lungs even though were normal on gross, showed medial hypertrophy of pulmonary vessels and plexogenic pulmonary arteriopathy characterised by capillary formation in the lumen of pulmonary vessels. These findings suggest pulmonary hypertension (Figure 5).

A large number of cirrhosis patients had no work up tailored towards screening for cardiomyopathy [43]. They should have screening for cardiac function once diagnosis is made and at least prior to a scheduled major procedure that can unmask the dysfunction and lead to serious morbidity or death [44]. Pregnancy and delivery were the precipitating stress factors in our patient and higher prevalence was noted in female gender.

## 6. Conclusion

Cirrhotic cardiomyopathy is often underdiagnosed. Awareness of cirrhotic cardiomyopathy is needed since implementation of angiotensin receptor blockers and beta blocker therapy early in the course of the cirrhosis may modify the changes in cardiac function. So that it will help to decrease the mortality rate in such patients.

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