Liver Cirrhosis in Woman with Ciliopathy Syndrome

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ABSTRACT

Ciliopathy syndrome is a congenital abnormality of structure and/or function of cilia, which causes pleiotropic disorder, including liver cirrhosis. This study aimed to describe a unique case of liver cirrhosis with possible aetiology of ciliopathy syndrome. A 44 year-old woman with chief complain of hematemesis had diabetes mellitus, obesity, dyslipidaemia, amenorrhoea and often became unconscious. We found short stature, brachydactyly, hyperpigmented maculae in trunk and four limbs, and hepatosplenomegaly. The laboratory results showed: haemoglobin 7.4 g/dl; albumin 2.42 g/dl; urea 84.8 mg/dl; creatinine 2.4 mg/dl; prolactin 138.8 ng/ml, while HBsAg was negative and anti-HCV was non-reactive. Abdominal ultrasonography showed liver cirrhosis; endoscopy showed grade 3 oesophageal varicose; FibroScan® showed 75 kPa; liver biopsy showed hydropic degeneration and cirrhosis; and head CT scan showed chronic lacunar infarction of corona radiata and mega cisterna magna occipital. We reported female with oesophageal varicose rupture, short stature, brachydactyly, obesity, diabetes mellitus, dyslipidaemia, hyperpigmented maculae, liver cirrhosis and mega cisterna magna, which was likely to suffer from ciliopathy syndrome.

Keywords: short stature, brachydactyly, insulin resistance, cirrhosis, ciliopathy.

INTRODUCTION

Rare aetiologies of liver cirrhosis include disorders.[1] One of the most rare aetiologies of liver cirrhosis associated with genetic disorders is the entity of cilia abnormality. Ciliopathy involves a variety of anatomical abnormalities.[2] Unfortunately, genetic examination is still out of reach due to lack of diagnosis tools in our country. Ciliopathy is rarely discussed in daily clinical practice because of its rarity, and will be discussed in this case report.

CASE ILLUSTRATION

A 44 year old unmarried woman from Javanese ethnic, worked as a tailor, was referred from private hospital to our hospital due to main complaint black tarry stool and bloody vomiting. She passed black tarry stool and vomited blood 2 days before admission, 3-4 times a day about a half glass volume each vomit. She did not feel any pain at her stomach, only bloating sensation and dizziness. She had similar condition one year earlier, had been hospitalised and got transfusion with packed red blood cells at that time. Since one year ago, she suffered enlarged abdomen, and after treated with medication, known by her as diuretics and some other drugs, her abdomen circumference gradually reduced. The patient never experienced a yellowish skin and tea like colour urine. Patient experienced itchy skin almost the entire body, especially her arms and legs; she often scratched it and leaving black spots on it.

She had suffered from diabetes mellitus since for four years before, and took oral anti-diabetes. She also often had high levels of blood

cholesterol. She complained temporary blurred vision and sometimes experienced fainting with unknown causes, and did not remember the incident before it. Several times she woke from fainting in various rooms at home including bathroom without anyone knowing and helping. Her menstrual period was irregular, and the last four months she did not have menstruation. She was short statured since childhood, and other family members who had short stature was her older sister. She was obese, but her weight slowly decreased since the last two years. She never consumed herbs, analgesics, alcohol and smoking.

At admission, she was moderate ill, fully conscious, blood pressure was 130/70 mmHg, pulse rate 70 beats per minute regular, respiratory rate 20 times per minute, axillary temperature 36 °Celsius, weight 50 kilograms, height 145 centimetres, and body mass index 24 kilograms/centimetres^2 (overweight). She looked anaemic and had asymmetric facial expression which we concluded as paresis of right nerve VII upper motor neuron type (**Figure1**). We found her had hepatomegaly with liver span of 14 cm, splenomegaly Schuffner 2, and shifting dullness test was positive which we concluded as ascites. She had short fingers and toes (*brachydactyly*) (**Figure 2**) and multiple hyperpigmented macules in the upper and lower extremities (**Figure 3**).

Abnormal laboratory findings were haemoglobin 7.4 g/dl, albumin 2.42 g/dl, urea 84.8 mg/dl, creatinine 2.4 mg/dl, prolactin 138.8 ng/ml, while HBsAg was negative and anti-HCV was non reative. Abdominal ultrasonography showed liver cirrhosis (**Figure 4**) and FibroScan® showed 75 kPa (F4). We conducted endoscopy, and it showed grade 3 oesophageal varicose (**Figure 5**). Liver biopsy showed hydropic degeneration and cirrhosis. We also conducted head CT scan with contrast because the patient had neurological deficits and often fainted, and it showed a chronic lacunar infarction at right corona radiata and mega cisterna magna occipital (**Figure 6**). We consulted the patient to Neurology Department to evaluate neurological problem. They diagnosed her with benign peripheral positional vertigo.

Figure 1. The patient's face looked asymmetry, concluded as paresis of right nerve VII upper motor neuron type.
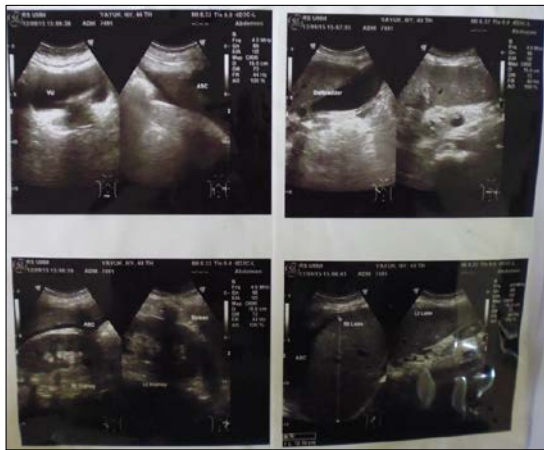

Figure 2. The fingers and toes of the patient were short (*brachydactyly*). The patient's stature is also short and obese.
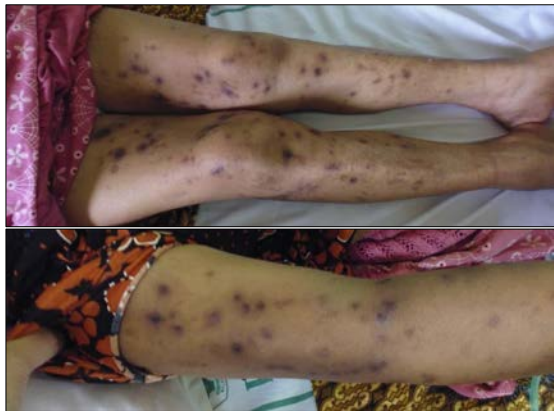
Figure 3. Upper and lower extremity of the patient had multiple hyperpigmented macules.
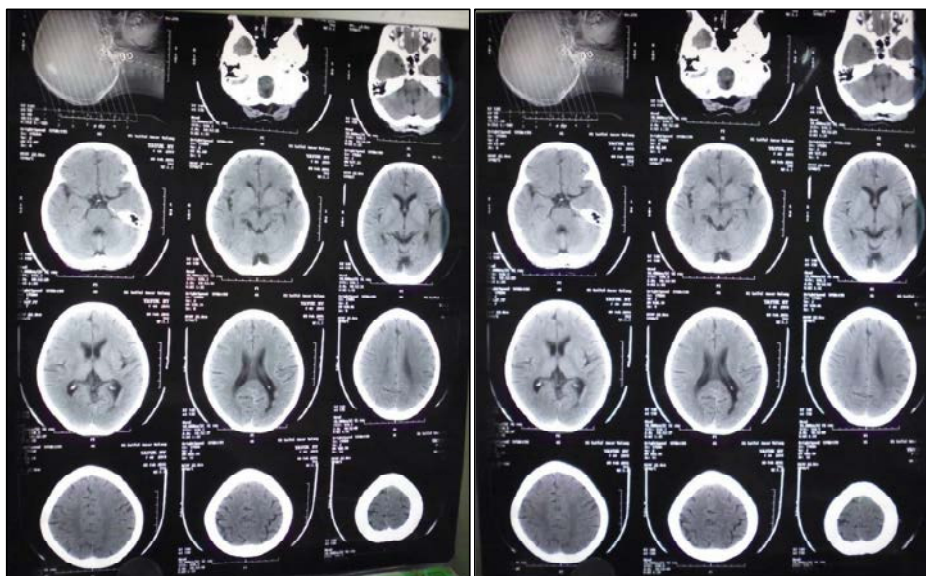

Figure 4. Abdominal ultrasonography showed liver cirrhosis with ascites.

Figure 5. Endoscopy showed grade 3 oesophageal varicose.

We treated the patient with octreotide bolus 50 mcg iv, continued with drip 50 mcg/hour, lansoprazol 30 mg iv every 12 hours, metoclopramide 10 mg iv every 8 hours, ceftriaxone 1 gram iv every 24 hours, insulin long acting 10 units subcutaneous at bed time, lactulose 1 table spoon 3 times a day, betahistine mesylate 24 mg pro re nata, PRC transfusion and albumin transfusion. After the hematemesis was resolved, we gave her propranolol 20 mg every 8 hours and spironolactone 100 mg a day. With several anatomical abnormality in this patient, we suspected her to had ciliopathy syndrome, but definitive diagnosis, gen abnormality, could not be performed due to lack of diagnostic tool in our hospital.

Figure 6. Head CT scan showed a chronic lacunar infarction at right corona radiata and mega cisterna magna occipital

DISCUSSION

Patient presented with hematemesis and melena. We found hepatosplenomegaly, abdominal ultrasonography described liver cirrhosis and FibroScan® showed high degree liver fibrosis. Generally, in hepatic cirrhosis, we find liver in smaller size. However, there are several conditions of liver cirrhosis with hepatomegaly, such as cardiac cirrhosis (Laennac cirrhosis) and fatty liver as seen in non-alcoholic fatty liver disease (NAFLD) that develops to liver cirrhosis.[3] Endoscopy revealed that she had grade 3 oesophageal varicose as the cause of hematemesis. This supported diagnosis of liver cirrhosis. Liver biopsy result was hydropic degeneration which was usually caused by hepatic cell injury. Chronic liver injury can cause cirrhosis and it is important to determine the specific aetiology given its implications in patient management and its long-term outcomes. Certainly, if the aetiology of a disease remains unknown, effective therapy can not be performed. We had excluded common aetiology of liver cirrhosis in the patient, such as viral hepatitis infection and autoimmune hepatitis. Epidemiologically, the most common aetiology of liver cirrhosis other than hepatitis viral infection is NAFLD, which usually revealed fatty degeneration on liver biopsy, but we found no fatty degeneration in the patient.[4,5] However, we considered that she had diabetes, dyslipidaemia and obesity. NAFLD is associated with metabolic syndrome and insulin resistance.[5,6] Obesity is common and well-documented risk factor for NAFLD.[4,5,6] There is a very high prevalence of NAFLD in individuals with type 2 diabetes mellitus. High serum triglyceride levels and low serum HDL levels are very common in NAFLD patients.[7] The prevalence of NAFLD in individuals with dyslipidaemia is estimated to be 50%.[8,9]

Although metabolic disorders such as obesity and type 2 diabetes are increasing in global pandemics, their pathophysiology and molecular basis are not fully understood.[8,9] The cause of obesity is complex, because many confusing genetic and environmental factors are not obviously affecting it.[6] In addition, metabolic disorders involve interconnected disease which can be exemplified by the association of obesity with insulin resistance, leading to the development of type 2 diabetes.[6,7] The genetic factors for obesity are poorly understood. Genomic association studies support the idea that some genes, tissues, and pathways, contribute to this disease. An interesting gene subsets associated with obesity are caused by primary ciliary dysfunction, resulting in a rare pleiotropic disorder in humans called ciliopathy syndrome.[8]

Primary cilia may act as sensory cell antennae, coordinating intercellular communications via receptor clustering and signalling.[10] Bardet-Biedl syndrome (BBS) is the archetypical example of a ciliopathy with profound appetite dysregulation. BBS children are unable to resist the drive to eat, becoming massively obese at an early age, and about half develop type 2 diabetes mellitus and metabolic syndrome. Another childhood obesity syndrome that may be ascribed to a ciliopathy is Alström syndrome (AS).[10,11] In addition to their respective specific features (skeletal, retinal, renal and hepatobiliary fibrocystic abnormalities, hearing defects and infertility), BBS and AS are both associated with hyperphagic obesity, early onset of insulin resistance, type 2 diabetes mellitus and (best described for AS) severe fatty liver disease leading to cirrhosis.[12] An additional exciting finding is that pre-adipocytes also express primary cilia, and these play a role in their capacity to differentiate and form triglyceride-storing adipocytes and secrete adiponectin.[11] The mice carrying a gene mutation for the basal body protein of cilia underwent NAFLD.[12,13] This is very appropriate with the condition of our patient who had characteristics of ciliopathy syndrome and also suffer from diabetes mellitus and history of obesity and dyslipidaemia.

It was very interesting that in this case, the patient also had body dysmorphism. She had asymmetrical facial expression, short stature and brachydactyly. Short stature and brachydactyly was also found in her older sister. She also suffered oligomenorrhea and even amenorrhoea in the last 4 months, had high level of serum prolactin and mega cisterna magna in the brain. We suggested that these abnormalities were related to one disease entity or syndrome and

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associated with her liver cirrhosis. When the structure or function of the cilia is defective, it affects most of the body's organs such as kidneys, brain, limbs, eyes, ears, liver and bones.[11,13,14] The unique characteristics of ciliopathy show a broad phenotypic spectrum determined by the degree of damage to the affected cilia and tissue specificity. The symptoms of ciliopathy vary greatly depending on the affected genes and their role in ciliogenesis and ciliary function.[10,11]

Cilia falls into two broad categories: motile and immotile.[10] Primary cilia are typically immotile and consist of nine peripheral doublet microtubules; while motile cilia, in addition, contain a central pair of singlet microtubules ("9+2" arrangement) to which they are connected by the radial spike proteins. Immotile cilia are characterised by the absence of the central pair of singlet microtubules ("9+0" arrangement).[11] Motile cilia are distinguished from primary cilia by their ability to beat rhythmically, an activity that is powered by adenosine triphosphate (ATP), hydrolysed by dynein proteins, which are anchored to the inner and outer aspects of peripheral doublet microtubules.[11,12] Motile cilia are utilised in both unicellular and multicellular organisms for locomotion. Primary cilia have chemosensory, osmosensory and phototransduction functions.[10,11,12]

As cilia are a component of almost all vertebrate cells, ciliary dysfunction can manifest as a constellation of features include congenital fibrocystic diseases of the liver and pancreas, diabetes, obesity and skeletal dysplasia.[10,11] Phenotypically heterogeneous, ciliopathic features can manifest from variation at a single locus while mutations affecting a number of different loci can, at the same time, result in similar phenotypes. Within each organ, diseases can be developmental phenotypes presenting at birth or later in childhood.[13] Often this may depend on the severity of the underlying mutation in addition to the number of defective proteins encoded where more than one mutation in a ciliary gene occurs.[14] Ciliary membranes contain receptors and ion channel proteins mediating cell signalling, including roles for Sonic Hedgehog (SHH), Wnt and PDGFa signalling pathways that control diverse

processes (e.g., cell differentiation, migration, axonal path finding, and planar cell polarity).[14] The SHH pathway is important for dorsal-ventral patterning of the neural tube and, later, for proliferation of cerebellar granule cells. Defects of this pathway can cause anomalies of the cerebral commissures.[15,16]

Intact cilia-based signalling is required for normal development of the biliary and portal system in the liver. The majority of diseases manifesting with hepatic fibrocystic pathology are caused by defective ciliary proteins.[12] Congenital hepatic fibrosis is a histopathological diagnosis with three main components; that is, defective remodelling of the ductal plate; abnormal portal veins; and progressive fibrosis of the portal tracks. The major morbidity associated with congenital hepatic fibrosis is portal hypertension.[12,13] Congenital fibrocystic diseases of the liver are a heterogeneous group of disorders that are characterised by a spectrum of biliary dysgenesis that includes congenital hepatic fibrosis, bile duct dilatation and cyst formation. Defects in cholangiocyte ciliary structure and/or their integrated transducing function lead to a decrease in intracellular calcium and increased cAMP, causing cholangiocyte hyperproliferation, abnormal cell matrix interactions and altered fluid secretion/absorption, which can result in hepatic cystogenesis.[13]

Emerging data indicate that hedgehog signalling, one of signalling pathway in primary cilia, mediates both adaptive and maladaptive responses to liver injury, depending upon the balance between its actions as a regulator of progenitor cell growth and its ability to promote liver inflammation and fibrogenic repair.[14] Synthesis of hedgehog ligands is stimulated by diverse factors that trigger liver regeneration, including both liver cell mitogens and liver cell stressors. These Hh ligands, in turn, are released from ligand-producing cells into the local environment where they engage receptors on Hh-responsive cells. The latter include progenitor cells, hepatic stellate cells, sinusoidal endothelial cells and certain types of resident hepatic immune cells. In general, Hh ligands function as trophic factors and promote the viability of Hh-target cells.[13,14] This enhances the outgrowth

of liver progenitor populations, triggers tissue remodelling, and promotes liver regeneration. However, Hh ligands also stimulate certain cell types (e.g., hepatic stellate cells, immature liver epithelial cells) to acquire a less epithelial and more mesenchymal state during which such cells generate inflammatory mediators and scar tissue, therefore, induces liver fibrogenesis. Hence, excessive or persistent Hh pathway activity actually aborts successful regeneration of damaged liver tissue and contributes to the pathogenesis of liver fibrosis.[14]

Findings of skin disorders in this patient led us to make the differential diagnosis of neurocutaneous disorder due to ciliopathy. Several case reports also presented skin disorders in patients with ciliopathy syndromes in the form of hyperpigmentation macules and sometimes also in the form of multiple nevus.[16,17,18] These skin disorders often coincided with pigmented abnormalities in the patient's cerebral meninges.[17,18] We tested the patient for serum prolactin level because of amenorrhoea. The condition of hyperprolactinemia in her could be caused by liver cirrhosis or stood alone. Hyperprolactinaemia could also be caused by her obesity.

Management of liver cirrhosis in patient with ciliopathy syndrome is same with that of other aetiology. The aetiology of cirrhosis in ciliopathy is related to development of NASH; so, the management of metabolic condition related to obesity and insulin resistance and dyslipidaemia should be optimized.

CONCLUSION

We reported woman with hematemesis, short stature, brachydactyly, hyperpigmented maculae, liver cirrhosis, and mega cisterna magna, which was likely to suffer from ciliopathy syndrome; however, genetic tests has not been performed on the patient yet. Management of patients with this syndrome is same as liver cirrhosis caused by other aetiology. Follow-up related to other organ abnormalities in the future, is necessary. Appropriate genetic counselling and family member screening should be performed. The definitive diagnosis necessarily requires chromosome and gene analysis, which is not available here.

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