Annals of Diagnostic Pathology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

Cholesteryl Ester Storage Disease: An underdiagnosed cause of cirrhosis in adults

Mamta Pant, Kiyoko Oshima *

Department of Pathology, Medical College of Wisconsin, Milwaukee, United States

ARTICLE INFO

Available online xxxx

Keywords:
Cholesteryl Ester Storage Disease
Wolman disease
Cirrhosis
Lysosomal storage disease
Lysosomal acid lipase deficiency

ABSTRACT

Cholesteryl Ester Storage Disease (CESD), is a rare multisystem autosomal recessive disorder and belongs to the broad family of lysosomal storage disorders. It can present anytime from infancy and childhood to even adulthood. The clinical manifestations are generally severe in infants and with milder forms in adults. One of the prominent sites of involvement is liver. Due to low awareness of this condition among physicians including surgical pathologists, majority of the liver biopsies, especially from the adults are often misdiagnosed as non-alcoholic fatty liver disease/non-alcoholic steatohepatitis or cryptogenic cirrhosis. Given the recent availability of safe and effective enzyme replacement therapy that can alter the natural course of CESD, the pathologists signing out adult and pediatric liver biopsies should be aware of this entity, thus contributing to timely patient management. This review discusses the clinical features, pathogenesis, diagnostic approach, differential diagnosis and management of CESD in adults.

Contents

1. Introduction

CESD, a lysosomal storage disease results from mutation of lysosomal acid lipase (LIPA) gene. LIPA gene mutation can cause either complete absence or near total deficient lysosomal acid lipase (LAL) activity. This results in two clinical phenotypes: Wolman disease (WD) and Cholesteryl Ester Storage Disease (CESD).

WD, the more severe phenotype results from complete LAL deficiency (absent or less than 1% LAL activity). The disease has an early onset in neonatal period/infancy. These children generally present around 2–4 months of age with vomiting, diarrhea, feeding difficulties, massive hepatosplenomegaly and adrenal calcifications. They have an aggressive clinical course and generally die within first 6–12 months of life [1,2].

In contrast, CESD is the milder subtype as it has some residual LAL activity (1–12% of normal). It can present in infancy, childhood or adulthood. Although the clinical presentation is variable, the typical features are hepatomegaly, elevated transaminases, elevated LDL-cholesterol and triglycerides and low HDL cholesterol. The liver biopsy shows diffuse microvesicular steatosis, liver fibrosis and or cirrhosis. CESD is

* Corresponding author at: Department of Pathology, Medical College of Wisconsin, Lab Building, 9200 W. Wisconsin Avenue, Milwaukee, WI 53226, United States.
E-mail address: koshima@mcw.edu (K. Oshima).

http://dx.doi.org/10.1016/j.anndiagpath.2017.02.005
1092-9134/

considered a rare disease. However, studies have shown that low awareness of this condition among physicians results in majority of the cases being either overlooked or misdiagnosed due to overlapping clinical and histological features with more commonly known entities like non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) and cryptogenic cirrhosis [2]. Currently, a recombinant enzyme replacement therapy (ERT) for LAL-deficiency is available and is under phase 3 clinical trial. The results of ERT are promising with definite decrease in disease related morbidity and mortality [3]. This makes it more important for surgical pathologists signing out liver biopsies be aware of this entity and consider it especially in the differential diagnosis of NAFLD or cryptogenic cirrhosis.

2. Clinical features

Current understanding of the disease process and clinical manifestations of CESD is largely based on the published single case reports, small series of case studies or literature review [2,4]. The clinical course is more variable in children and adults than in infants [5]. Onset of symptoms can vary from birth until 44 years in males and 68 years in females, however the reported mean age is 5 years in both males and females. Severely affected patients usually present in infancy and have WD like clinical manifestation [2]. However, the most consistent findings seen in almost all age groups are hepatic dysfunction and lipid abnormalities [5]. Hepatomegaly is present in ~99% cases. Findings can vary from severe liver disease in early childhood to only serum transaminase elevation or these patients remain asymptomatic until adulthood and silently progress to liver fibrosis and cirrhosis as seen on liver biopsies performed to investigate the etiology of liver enzyme abnormality. Studies have also shown that liver fibrosis and or cirrhosis develops at a relatively early age and its frequency is also relatively high compared to other chronic liver diseases [4,6]. This suggests that lysosomal accumulation of cholesteryl esters and triglycerides is a potent inducer of liver fibrosis [6]. These patients are also commonly referred to the lipid clinic for accelerated atherosclerosis or premature cardiovascular disease and have elevated total cholesterol, LDL-cholesterol, triglycerides and decreased HDL-cholesterol [2,5]. More variable manifestations include splenomegaly (~74%) likely secondary to portal hypertension or lipid retention, esophageal varices, recurrent abdominal pain, diarrhea especially in children due to small intestinal lipid retention, malabsorption, anemia and short stature [7]. Most common cause of death is liver failure [2].

3. Pathogenesis

LAL is a 46Kda lysosomal glycoprotein that normally hydrolyzes low density lipoprotein (LDL) derived cholesteryl esters and triglycerides into free cholesterol and free fatty acids in the lysosomes. The free cholesterol is transferred from lysosomes to cell membrane where it plays a key role in cellular cholesterol homeostasis. It down-regulates LDL receptors leading to reduced entry of cholesterol into the cells. It suppresses activity of HMG-coenzyme A reductase, reducing cholesterol synthesis [8]. It also controls the activity of ATP-binding cassette transporter A1 (ABCA1) thus regulating HDL production [3,9]. LAL is synthesized by almost all cells and tissues of the human body and is encoded by lysosomal acid lipase gene.

Deficient activity of LAL leads to failure of degradation and systemic accumulation of cholesteryl ester and triglycerides within the lysosomes of various tissues and cell types, predominantly liver [2]. The reduced generation of free intracellular cholesterol in turn upregulates cholesterol synthesis via HMG-coenzyme A reductase, increases cholesterol uptake by body cells via LDL receptors and decreases activation of ABCA1 expression reducing formation of HDL cholesterol. This results in dyslipidemia with elevated serum total and LDL cholesterol, high triglycerides and low HDL cholesterol. The progressive accumulation of cholesteryl esters and triglycerides within lysosomes is a potent inducer of fibrosis. This leads to increased frequency and early development of hepatic fibrosis and or cirrhosis in these patients [2,5,6].

4. Genetics and epidemiology

LAL-deficiency (LAL-D) results from genetic mutations of the LIPA gene. This is a ~36 kb gene containing 10 exons and mapped on chromosome 10q23.2–q23.3 [2,5,10]. Individuals presenting with LAL-D are either homozygous or compound heterozygous for LIPA mutations. More than 40 loss-of-function LIPA mutations have been identified in CESD and WD. In WD, majority of the mutations are predicted to produce a stop codon, resulting in truncated protein with almost absent LAL activity [5]. In CESD, of the 32 described mutations, majority are missense, with small percentage of small deletions/insertions, nonsense, consensus splice-site mutations and large deletions. However, the most common mutation seen only in CESD and accounting for more than 50% of all CESD mutations is exon 8 splice junction mutation, E8SJM (c.894g>A) [2,10]. This mutation causes alternative splicing leading to in-frame deletion of exon 8. The resultant mutant enzyme has no LAL activity, however small amount of LIPA pre-mRNA is spliced correctly resulting in 3–5% residual LAL activity [2,11]. Hence the clinical presentation in CESD is much milder compared to the fulminant presentation of WD.

Due to its rarity or possibly under-recognition, the frequency and prevalence of CESD is largely unknown [2,5]. A German study estimated E8SJM allele frequency of 0.0025 (1 in 202 carrier frequency), thus predicting a prevalence of ~2.4 per 100 000 [12]. A recent US study on healthy multiracial, multiethnic adults estimated c.894G>A allele frequency of 0.0017 in US Caucasian and Hispanic (carrier frequency ~1 in 300; predictive prevalence of ~0.8 per 100 000), 0.0005 in Asians (carrier frequency ~1 in 1000) with no heterozygotes seen in African-Americans [10]. These findings indicate that CESD is definitely underdiagnosed in general Caucasian and Hispanic population. As E8SJM in not common in Asians and African population, a full-gene LIPA sequencing is required to determine CESD prevalence and heterozygote frequency [10].

5. Diagnosis

CESD should be suspected in patients clinically presenting with hepatomegaly, elevated transaminases, elevated total and LDL cholesterol and triglycerides and low HDL cholesterol and with abnormal liver biopsy findings of diffuse microvesicular steatosis and or fibrosis or cirrhosis. Confirmation is based on demonstration of deficient LAL enzyme activity and or presence of LIPA gene mutation [2].

5.1. Liver pathology

Liver on gross examination has a diffuse bright yellow-orange appearance due to lysosomal lipid accumulation [7]. Microscopically, the most striking and consistent finding is the presence of diffuse microvesicular steatosis with lipid accumulation within lysosomes of hepatocyte, Kupffer cells and portal macrophages [2,7] (Fig. 1A, B). The Kupffer cells and portal macrophages also have ceroid accumulation which are highlighted by PAS after diastase stain. PAS stain shows decreased glycogen in hepatocytes (Fig. 1C). The presence of microvesicular steatosis however is not specific for CESD. It can be seen with other more common entities plus routine histologic stains cannot differentiate lysosomal from cytosolic lipid accumulation [13]. Additional findings may include presence of liver fibrosis (portal/periportal, sinusoidal or septal fibrosis) and or cirrhosis (Fig. 1D). Studies have shown that approximately 16% patients show histologic evidence of liver fibrosis and or cirrhosis on the first biopsy, at a mean age of only 13 years [2,4]. Pathognomonic clue to the diagnosis of CESD on tissue sections includes the demonstration of birefringent cholesteryl ester crystals in hepatocytes and Kupffer cells on fresh frozen liver sections under polarizing light [2,14]. In fixed paraffin

Please cite this article as: Pant M, Oshima K, Cholesteryl Ester Storage Disease: An underdiagnosed cause of cirrhosis in adults, Annals of Diagnostic Pathology (2017), http://dx.doi.org/10.1016/j.anndiagpath.2017.02.005