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An Adolescent with Chanarin-Dorfman Syndrome Presenting with Ichthyosis and Hepatic Steatosis

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Abstract: Chanarin-Dorfman syndrome also known as neutral lipid storage disease is a rare multisystemic autosomal recessive disorder. It is mostly encountered in patients of Mediterranean and Middle Eastern origin. Most patients are brought to medical attention secondary to dermatological manifestations namely ichthyosis. Here, we report a 10-year-old Kurdish male patient with ichthyosis, who was referred to pediatric liver clinic for transaminase elevation of unknown etiology despite elaborate workup. Histological findings on liver biopsy were consistent with nonalcoholic steatohepatitis. Genetic testing identified homozygous mutation C.776G>A (p.G259D) in the Abhydrolase domain containing 5 gene on chromosome 3 described in patients with Chanarin-Dorfman syndrome. After the initiation of a diet with high medium chain triglycerides/long chain triglycerides ratio, aerobic exercise, and vitamin E, the patient liver enzymes improved. Due to debilitating ichthyosis, he was started on acitretin therapy that was discontinued due to transaminases elevation. Patient is currently stable and doing well.

Key Words: fatty liver disease, neutral lipid storage disease

INTRODUCTION

Chanarin-Dorfman syndrome (CDS) also known as neutral lipid storage disease is a rare multisystemic autosomal recessive disorder with less than 100 cases reported in the literature. It is commonly encountered in patients of Mediterranean origins (1,2). CDS is an inborn error of metabolism associated with ichthyosis (a heterogeneous group of disorders characterized by pathological scaling of the skin), liver involvement, and developmental delay. The disease arises from mutation involving the ABHD5 gene on chromosome 3 culminating in dysfunction in adipose triglyceride lipase (ATLG) enzyme, which is instrumental in triglyceride metabolism (3).

CASE REPORT

A 12-year-old male patient with congenital ichthyosis was referred by dermatology to the pediatric liver clinic at the age of 10 years for evaluation of new onset elevation in transaminases (alanine aminotransferase [ALT] 171 U/L-normal <55 U/L, aspartate aminotransferase [AST], 103 U/L-normal <60 U/L). He was born following an uncomplicated pregnancy to healthy parents who are consanguineous Iraqi Kurds. Notably, the patient had elevated creatine kinase (1048 U/L-normal < 198 U/L) in the absence of myopathy.

The patient had a lean body habitus (weight, 42.6 kg [77th percentile]; height, 145.5 cm [88th percentile]; body mass index, 20.12 kg/m^2 [88th percentile] using CDC growth charts). Diffuse ichthyosis and erythroderma were notable. No evidence of ectropion or cataracts were noted. His ears were filled with cerumen. He had a systolic murmur left to the sternum. His abdomen was soft. An enlarged liver was palpable below the right costal margin (5.5 cm). No splenomegaly was appreciated. Neuropsychiatric assessment was notable for a normal neurological exam, age synchronous developmental milestones, anxiety, and depression.

Evaluation for etiologies of chronic elevation of transaminases was unremarkable including viral infections (hepatitis A, B and C, CMV, EBV), celiac disease, thyroid dysfunction, and metabolic disorders (serum amino acids, urinary organic acids, Transferrin isoelectric focusing for congenital disorder of glycosylation, carnitine, and acyl-carnitine profile). Markers of hepatobiliary function were normal including, bilirubin, prothrombin time, and albumin. Biliary enzymes were within normal range, and transaminases were elevated (ALT 171 U/L-normal <55 U/L, aspartate aminotransferase [AST] 103 U/L-normal <60 U/L). A complete blood count with peripheral smear revealed vacuolation of granulocytes due to lipid accumulation (Jordan's anomaly). An abdominal ultrasonography showed hepatic steatosis. A liver biopsy and noninvasive hepatic fibrosis assessment with FibroScan showed mild (25%) macrovesicular steatosis and chronic lymphocytic predominant inflammation with focal zone 3 perisinusoidal and pericellular fibrosis (stage 1 of 4, Fig. 1)

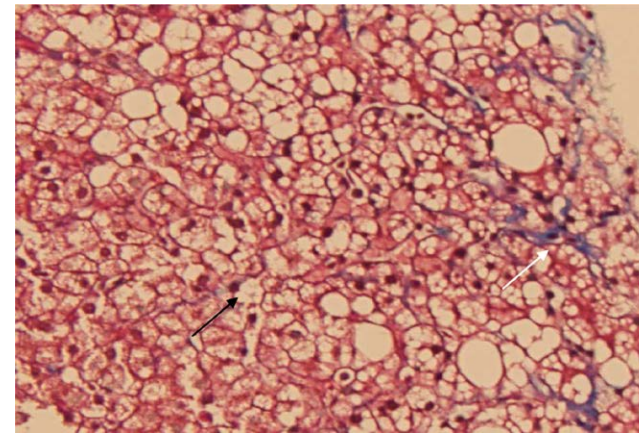

FIGURE 1. Liver biopsy with hematoxylin and eosin stain showing areas of steatosis (black arrow) with pericellular and perisinusoidal fibrosis (white arrow).

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The parents or guardian of the child in question are aware of this case report and they have given their consent
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and Stage 2 fibrosis with a median liver stiffness score of 8.7 kilopascal (kPa) respectively. The echocardiography was normal.

Given the history, consanguinity and the multisystemic involvement (ichthyosis, elevated transaminases, hepatic steatosis with fibrosis, Jordan's anomaly), the patient was referred to medical genetics. Genetic testing (XomeDxSlice—Congenital Ichthyosis gene panel Genedx) showed homozygous mutation C.776G>A (p.G259D) in the ABHD5 gene. A mutation well described in the literature to cause CDS.

The patient had persistent elevation of transaminases on serial testing. Repeat FibroScan at the age of 12 years showed median liver stiffness score of 16.5 kPa consistent with advanced hepatic fibrosis. The patient was started on Vitamin E (400 IU twice daily) and a diet with high MCT/LCT ratio (4,5). Dermatology later started him on low-dose oral acitretin (10 mg/day) for his ongoing ichthyosis. The patient's hepatic biochemical profile worsened on acitretin (increase in transaminases and bilirubin). Acitretin was eventually discontinued leading to improvement in liver laboratory tests .

DISCUSSION

Typical features of CDS are variable but include dermatologic (ichthyosis—a hallmark of the disease), neuropsychiatric (developmental delay and behavioral disturbances, including anxiety), ophthalmologic (cataracts, ectropion), auditory (sensorineural and conductive hearing loss), cardiac (hypertrophic cardiomyopathy, left ventricular hypertrophy), gastrointestinal (steatotic liver disease), musculoskeletal (myalgia, myopathy, elevation in creatine kinase), endocrine (hypothyroidism and short stature) among less common features (2).

Typical biochemical findings in CDS include increased serum creatine kinase, hepatic transaminases, and the presence of Jordan's anomaly on blood smear. Other findings include rhythm abnormalities on electrocardiogram and cardiomyopathy with lipid infiltration of the myocardium (2).

Our patient exhibited typical features of CDS including integumentary, hepatic, and neuropsychiatric symptoms (depression, anxiety, and learning difficulty). He also developed conductive hearing loss due to cerumen impaction. Slit-lamp exam was unremarkable.

The management and natural history of CDS are not well defined. A retrospective study involving 21 patients with CDS revealed normal life expectancy but a reduced quality of life likely secondary to intense pruritus, depression, and deafness (2).

A multidisciplinary team approach is of paramount importance when managing patients with CDS. Few treatment strategies have been described including dietary interventions (diet with high MCT/LCT ratio). For the management of steatosis and NASH, vitamin E has been described and liver transplantation for end stage liver disease (2,5). Our patient was started on vitamin E 400 IU twice daily and a diet with a high MCT/LCT ratio.

Patients with CDS are prone for drug-induced liver injury. A notable example is the use of systemic retinoids for the management of ichthyosis. Hepatotoxicity is a known and dreaded side effect of acitretin. Its use in patients with CDS has been described with improvement in dermatological and hepatic manifestations (6). In our patient, the opposite effect was noted with worsening of his biochemical profile and acitretin was subsequently discontinued.

CDS, while rare, should be considered in a patient with lean NASH in the appropriate clinical setting (i.e., ichthyosis in a patient of Middle Eastern ancestry). Given the rarity of this condition no standard of care is available. Measures to ameliorate symptoms and halt disease progression include manipulation of diet, topical and systemic retinoid derivatives for ichthyosis and vitamin E for NASH/NAFLD. Liver biochemical profile should be monitored closely for drug induced liver injury, particularly while using systemic retinoids.

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