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CASE REPORT
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Progressive familial intrahepatic cholestasis type 3 (PFIC3), a rare chronic liver disease: A case report

Fulden Kavas Coşkuner,[1] Tuğba Kazmacan,[1] Burcu Yeter,[2] Nelgin Gerenli[1]

[1]Divison of Hepatology and Nutrition Unit, Department of Pediatric Gastroenterology, University of Health Sciences, Ümraniye Training and Research Hospital, İstanbul, Türkiye
[2]Department of Pediatric Genetics, University of Health Sciences, Ümraniye Training and Research Hospital, İstanbul, Türkiye

ABSTRACT

Progressive familial intrahepatic cholestasis type 3 (PFIC3) is a rare autosomal recessive chronic liver disease characterized by reduced secretion of bile phospholipids resulting from pathogenic variants in the *ABCB4* gene. In pediatric cases, it typically presents with jaundice, pruritus, hepatosplenomegaly, and elevated GGT levels and may progress to cirrhosis and liver failure with advancing age. This study presents a pediatric case diagnosed with PFIC3. A 7.5-year-old female patient presented with jaundice, fatigue, and pruritus. Physical examination revealed an icteric appearance, hepatosplenomegaly, and findings consistent with chronic liver disease. Laboratory findings showed cholestasis and elevated liver enzyme levels. Imaging studies also revealed findings consistent with chronic liver disease. Liver biopsy revealed inflammation, fibrosis, and a reduction in the number of bile ducts. Genetic testing identified compound heterozygous variants in the *ABCB4* gene, one of which was pathogenic and the other a variant of uncertain significance (VUS). In conclusion, genetic analysis is critically important in the diagnosis of PFIC3, alongside clinical, laboratory, and histopathological findings. Screening other family members is important for early diagnosis, disease management, and prognosis.

Keywords: *ABCB4*; child; cholestasis; PFIC3.

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Correspondence (İletişim): Dr. Fulden Kavas Coşkuner. Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi, Pediatrik Gastroenteroloji Anabilim Dalı, Hepatoloji ve Beslenme Kliniği, İstanbul, Türkiye.
Phone (Tel): +90 537 323 82 01 **e-mail (e-posta):** fuldenkvs@gmail.com

Progresif familyal intrahepatik kolestaz tip 3 (PFIC3), nadir görülen kronik bir karaciğer hastalığı: Olgu sunumu

ÖZET

Progresif familyal intrahepatik kolestaz tip 3 (PFIC3), *ABCB4* genindeki patojenik varyantlara bağlı olarak gelişen, safra fosfolipit sekresyonunun azalmasıyla karakterize, nadir görülen ve otozomal resesif kalıtım gösteren kronik bir karaciğer hastalığıdır. Pediatrik olgularda genellikle sarılık, hepatosplenomegali, kaşıntı ve yüksek GGT düzeyleriyle seyreder ve ilerleyen yaşlarda siroz ve karaciğer yetmezliğine ilerleyebilir. Bu çalışmada, PFIC3 tanısı alan pediatrik bir olgu sunulmuştur. Yedi buçuk yaşında kız hasta, sarılık, halsizlik ve kaşıntı şikâyetleriyle başvurdu. Fizik muayenesinde ikterik görünüm, hepatosplenomegali ve kronik karaciğer hastalığı bulguları saptandı. Laboratuvar incelemelerinde kolestaz ve karaciğer enzim yüksekliği görüldü. Görüntüleme yöntemlerinde de kronik karaciğer hastalığını destekleyen bulgular izlendi. Karaciğer biyopsisinde inflamasyon, fibrozis ve safra duktuslarında azalma saptandı. Genetik incelemede *ABCB4* geninde patojenik bir varyant tespit edilerek PFIC3 tanısı doğrulandı. Sonuç olarak, PFIC3 tanısında klinik, laboratuvar ve histopatolojik bulgularla birlikte genetik analizler de kritik öneme sahiptir. Ailenin diğer bireylerinin de taranması, erken tanı, hastalık yönetimi ve prognoz açısından önemlidir.

Anahtar Kelimeler: *ABCB4*; çocuk; kolestaz; PFIC3.

ORCID ID

FKC: 0000-0002-8689-4791; TK: 0000-0002-1307-5541; BY: 0000-0002-6255-1057; NG: 0000-0002-2395-163X

[1]Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi, Pediatrik Gastroenteroloji Anabilim Dalı, Hepatoloji ve Beslenme Kliniği, İstanbul, Türkiye
[2]Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi, Pediatrik Genetik Anabilim Dalı, İstanbul, Türkiye

INTRODUCTION

Progressive familial intrahepatic cholestasis type 3 (PFIC3) is a chronic liver disease inherited in an autosomal recessive pattern, caused by pathogenic variants in the *ABCB4* gene, and characterized by reduced bile phospholipid secretion due to MDR3 protein deficiency (1, 2). Although the prevalence of the disease is not precisely known, it is estimated to account for approximately 10–15% of all cases of cholestasis observed in children (3). In pediatric cases, the clinical presentation typically includes jaundice, hepatomegaly, splenomegaly, pruritus, and acholic stools, along with elevated serum GGT levels on laboratory testing. Most patients develop cirrhosis, portal hypertension (PHT), and liver failure within the first 20 years of life (1, 4). In the differential diagnosis, infections in early childhood, as well as metabolic disorders such as Alagille syndrome, Wilson disease, autoimmune hepatitis, primary sclerosing cholangitis, cystic fibrosis, tyrosinemia, Gaucher disease, and glycogen storage diseases (types 3 and 4), should be considered and ruled out. Ursodeoxycholic acid (UDCA) is used for treatment, and studies have reported that UDCA improves liver survival (4). As progressive liver fibrosis, cirrhosis, and end-stage liver disease develop, liver transplantation becomes necessary (2).

CASE REPORT

A 7.5-year-old female patient with no known chronic illness presented with jaundice, fatigue, and pruritus. Physical examination revealed icteric skin and sclerae, facial telangiectasias, digital clubbing, and palmar erythema. Abdominal examination revealed hepatomegaly with hypertrophy of the left lobe and splenomegaly. The patient also had growth and developmental delay; her height was 115 cm (-1.9 SDS), and her weight was 19 kg (-1.7 SDS). Laboratory findings included a WBC count of 7,610/mm³, hemoglobin (Hb) level of 12.7 g/dL, mean corpuscular volume (MCV) of 91 fL, platelet (PLT) count of 132,000/mm³, alanine aminotransferase (ALT) level of 143 U/L, aspartate aminotransferase (AST) level of 275 U/L, albumin level of 3.8 g/dL, total bilirubin level of 3.3 mg/dL, direct bilirubin level of 3 mg/dL, gamma-glutamyl transferase (GGT) level of 353 U/L, creatine kinase (CK) level of 61 U/L, erythrocyte sedimentation rate (ESR) of 99 mm/h, prothrombin time of 16 seconds, INR of 1.2, total cholesterol level of 155 mg/dL, and HDL level of 13 mg/dL. Autoantibodies associated with autoimmune hepatitis, including anti-LKM-1, AMA, and ASMA, were negative. Portal Doppler ultrasonography revealed that the liver was enlarged to 120 mm. The parenchymal echotexture was heterogeneous and granular, and multiple hypoechoic nodular lesions were observed, the largest of which measured 10 mm in diameter. The portal vein diameter was normal, and blood flow was hepatopetal. The spleen was enlarged (118×54 mm), the sinusoids were prominent, and the splenic vein diameter and blood flow direction were reported as normal. Linear hyperechoic structures were also observed. Whole-abdominal MRI revealed enlargement of the left hepatic lobe, hypertrophy of the caudate lobe, and millimeter-sized hypointense nodular lesions in the parenchyma. These lesions were considered possible dysplastic nodules that had developed against a background of chronic liver disease. A liver biopsy was planned to determine the etiology of

Table 1. Molecular and clinical characteristics of variants identified in the *ABCB4* gene

Gene/transcript	Genomic position (hg19)	Variant (cDNA/protein)	Annotation	Zygosity	ACMG classification	ClinVar ID
ABCB4 NM_000443.4	Chr7:87069514 –	c.1560+1G>A	Intronic	Heterozygous	Pathogenic (PVS1, PM2, PP5)	1676065
ABCB4 NM_000443.4	Chr7:87082270 Exon 6	c.526C>T p.Arg176Trp	Missense	Heterozygous	VUS (PM2, PP5)	372802

VUS: Variant of uncertain significance.

the patient's chronic liver disease. Histopathological examination revealed mild-to-moderate inflammation in all portal areas, periportal and periseptal interface hepatitis (moth-eaten necrosis), and fibrosis extending into the portal areas, along with findings consistent with bile duct hypoplasia and glycogenosis. During the genetic evaluation, the patient underwent targeted PFIC panel analysis based on clinical exome sequencing (CES). Compound heterozygous variants in the *ABCB4* gene were identified, one of which was pathogenic and the other was a variant of uncertain significance (VUS) (Table 1). Because the patient voluntarily discontinued outpatient follow-up at our clinic, no additional information is available regarding her long-term prognosis or current clinical status.

Written informed consent was obtained from the patient's legal representative for publication of this case report and the accompanying clinical information.

CONCLUSION

Our case highlights the importance of considering PFIC3, a rare liver disease, in the differential diagnosis of patients presenting with signs of cholestasis. Establishing a definitive diagnosis requires molecular and genetic analyses as well as clinical, laboratory, and histopathological evaluations. Furthermore, screening other family members and providing genetic counseling are essential for early diagnosis and disease management.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient's legal representative for publication of this case report and the accompanying clinical information.

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Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemiştir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Olgu sunumunun hazırlanması sırasında yazarlar, yazı dilini düzeltme ve taslak hazırlama desteği için yapay zeka (AI) destekli teknolojilerden yararlanmış olup, nihai olarak tüm içerik yazarlar tarafından incelenmiş, düzenlenmiş ve onaylanmıştır.

Yazarlık Katkıları: Fikir – FKC, NG; Tasarım – FKC, TK; Denetlemeler – FKC, NG; Kaynaklar – FKC; Malzemeler – FKC; Veri toplanması ve/veya işleme – FKC, NG; Analiz ve/veya yorumlama – FKC; Literatür araştırması – FKC; Yazım – FKC; Eleştirel incelemeler – FKC; Genetik Analiz – BY.

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