Consent for publication

No details, images, or videos relating to an individual person contained so no specific consent required.

Acknowledgements

None.

References

[1] Ma H, Xu C-F, Shen Z, Yu C-H, Li Y-M. Application of machine learning techniques for clinical predictive modeling: a cross-sectional study on nonalcoholic fatty liver disease in China. Biomed Res Int 2018;2018:4304376.
[2] Kuppili V, Biswas M, Sreekumar A, Suri HS, Saba L, Edla DR, et al. Extreme learning machine framework for risk stratification of fatty liver disease using ultrasound tissue characterization. J Med Syst 2017;41(August (10)):152.
[3] Byra M, Styczynski G, Szmigielski C, Kalinowski P, Michałowski Ł, Paluszkiewicz R, et al. Transfer learning with deep convolutional neural network for liver steatosis assessment in ultrasound images. Int J Comput Assist Radiol Surg 2018;13(December (12)):1895–903.
[4] Biswas M, Kuppili V, Edla DR, Suri HS, Saba L, Marinhoe RT, et al. Symtosis: a liver ultrasound tissue characterization and risk stratification in optimized deep learning paradigm. Comput Methods Programs Biomed 2018;155:165–77.
[5] Cristoferi L, Nardi A, Ronca V, Invernizzi P, Mells G, Carbone M. Prognostic models in primary biliary cholangitis. J Autoimmun 2018;95(December):171–8.
[6] Bertsimas D, Kung J, Trichakis N, Wang Y, Hirose R, Vagefi PA. Development and validation of an optimized prediction of mortality for candidates awaiting liver transplantation. Am J Transplant 2018;(November).
[7] Briceño J, Cruz-Ramírez M, Prieto M, Navasa M, Ortiz de Urbina J, Orti R, et al. Use of artificial intelligence as an innovative donor-recipient matching model for liver transplantation: results from a multicenter Spanish study. J Hepatol 2014;61(November (5)):1020–8.
[8] Dou Q, Yu L, Chen H, Jin Y, Yang X, Qin J, et al. 3D deeply supervised network for automated segmentation of volumetric medical images. Med Image Anal 2017;41(October):40–54.
[9] Ibragimov B, Toesca D, Chang D, Yuan Y, Koong A, Xing L. Development of deep neural network for individualized hepatobiliary toxicity prediction after liver SBRT. Med Phys 2018;45(October (10)):4763–74.
[10] Saini N, Bakshi S, Sharma S. In-silico approach for drug induced liver injury prediction: recent advances. Toxicol Lett 2018;295(October):288–95.

Christopher A. Lovejoy [a,b,*]
[a] *Cera Care, London, United Kingdom*
[b] *St George's Hospital, London, United Kingdom*

Bruce Keogh
Birmingham Women's and Children's Hospital NHS Foundation Trust, United Kingdom

Mahiben Maruthappu
Cera Care, London, United Kingdom

* Corresponding author at: St George's Hospital, Blackshaw Road, London SW17 0QT, United Kingdom.
E-mail address: christopher.lovejoy1@gmail.com (C.A. Lovejoy)

21 June 2019

https://doi.org/10.1016/j.dld.2019.06.018

Fanconi syndrome due to tenofovir disoproxil fumarate (TDF) after liver transplantation

To the Editor

A 55 year-old man with a previous medical history of hepatitis B virus (HBV) and hepatitis D virus (HDV) infection with decompensated cirrhosis underwent liver transplant (LT) in June 2018. Two weeks after an uneventful liver transplant the patient was taking tacrolimus 9 mg/day, mycophenolate mofetil 360 mg/12 h and prednisone 10 mg/day as part of immunosuppressive therapy, cotrimoxazole 160/800 mg/day, calcium/vitamin D, folic acid 5 mg/day, enalapril 5 mg/day, insulin and TDF 245 mg/day, the latter as a prophylaxis for hepatitis B. Serum creatinine (Cr) and glomerular filtration rate (GFR) at the last outpatient clinic control (July 2018) were 1.03 mg/dl and 81 ml/min, respectively.

In October 2019, four months after LT, laboratory follow-up showed an abnormal renal function (Cr 1.50 mg/dl; GFR 52 ml/min), and the patient referred mild neurological symptoms (tremor, lack of concentration). Due to the suspicion of tacrolimus toxicity the drug was replaced by everolimus (0.75 mg/b.i.d.). Nevertheless, renal function continued to worsen and the patient was finally admitted to our hospital. Laboratory tests showed Cr 1.73 mg/dl and GFR 44 ml/min; 24-h urine showed proteinuria (2.035 g), hyperphosphaturia (1.4 g) glucosuria (14.3 g) and uricosuria (1.1 g). Kidney ultrasound ruled out morphological alterations and renal artery stenosis.

After the later results, highly suggestive of renal tubular damage, the patient was diagnosed with Fanconi syndrome secondary to TDF. TDF was switched to entecavir and the patient was discharged. Three months after discharge renal function had normalized (Cr was 1.2 mg/dl, GFR 62 ml/min) and 24-h urine phosphate and uric acid were also within normal ranges. 24-h urine glucose and protein still remained elevated (2.4 g and 0.179 g per day, respectively), though significantly lower than at hospital admission.

TDF is a nucleotide analogue used since 2001 for treatment of HIV and HBV infection. Renal tubular dysfunction during long-term adefovir or tenofovir therapy in chronic hepatitis B is well known and some patients may develop renal failure, usually mild [1,2]. The degree of association between TDF treatment and changes in markers of renal function/tubular damage vary among studies; discrepancies may result from the use of different definitions and cut-offs for reporting renal toxicity [3].

Fanconi syndrome, an inadequate reabsorption in the proximal renal tubules of the kidney, is caused by various underlying congenital or acquired diseases, and has been associated with drug toxicity. The syndrome has been described in HIV-infected patients who are under TDF, probably due to a combination of TDF toxicity and the use of concomitant antiretroviral drugs. A review of the FDA Adverse Event Reporting System from 2001 to 2006 identified 164 TDF-treated HIV-infected patients with Fanconi syndrome, 83% of which received protease inhibitors [4]. Contrarily, there are very few reported cases of Fanconi syndrome in HBV monoinfected patients treated with tenofovir. In a review article published on 2016 only 8 cases were identified [3] and we only found 5 additional cases of Fanconi syndrome due to TDF in chronic HBV-monoinfected patients [5–9], including a case of early renal injury in a pediatric patient treated for acute hepatitis B [9]. Despite its extremely low incidence, Fanconi syndrome should be suspected in liver transplant patients on TDF with signs of tubular damage. As recommended by the recently published EASL Clinical Guidelines [10], patients treated with TDF should undergo periodical renal monitoring including at least GFR and serum phosphate levels. The concomitant use of nephrotoxic drugs in transplant recipients (i.e. immunosupressants) may be a facilitating factor for TDF toxicity. In such cases, treatment should be immediately changed to tenofovir alafenamide or entecavir.

Conflict of interest

XF has acted as advisor for Gilead and Abbive. JC declares lectures paid by Gilead.

References

[1] Gara N, Zhao X, Collins MT, Chong WH, Kleiner DE, Jake Liang T, et al. Renal tubular dysfunction during long-term adefovir or tenofovir therapy in chronic hepatitis B. Aliment Pharmacol Ther 2012;35:1317.

[2] Wong GL, Tse YK, Wong VW, Yip TC, Tsoi KK, Chan H. Long-term safety of oral nucleos(t)ide analogs for patients with chronic hepatitis B: a cohort study of 53,500 subjects. Hepatology 2015;62:684–93.
[3] Lampertico P, Chan HL, Janssen HL, Strasser SI, Schindler R, Berg T. Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients. Aliment Pharmacol Ther 2016;44:16–34.
[4] Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. AIDS Patient Care STDS 2008;22:99–103.
[5] Suh YS, Chun DI, Choi SW, Lee HW, Nho JH, Kwon SH, et al. Pathologic femoral fracture due to tenofovir-induced Fanconi syndrome in patient with chronic hepatitis B. Medicine (Baltimore) 2017;96:46.
[6] Grossi G, Loglio A, Facchetti F, Borghi M, Soffredini R, Galmozzi E, et al. Tenofovir alafenamide as a rescue therapy in a patient with HBV-cirrhosis with a history of Fanconi syndrome and multidrug resistance. J Hepatol 2018;68:195–8.
[7] Kim D, Lee J, Kim DH, Kang K, Suh SJ, Jung YK, et al. A case of tenofovir-associated fanconi syndrome in patient with chronic hepatitis B. Korean J Gastroenterol 2016;68:317–20, http://dx.doi.org/10.4166/kjg.2016.68.6.317.
[8] López Centeno B, Collado Borrell R, Pérez Encinas M, Gutiérrez García ML, Sanmartin Fenollera P. Comparison of the effectiveness and renal safety of tenofovir versus entecavir in patients with chronic hepatitis B. Farm Hosp 2016;40:279–86.
[9] Pascale R, Guardigni V, Badia L, Volpato F, Viale P, Verucchi G. Early onset of tenofovir-related fanconi syndrome in a child with acute hepatitis B: a case report and systematic review of literature. Case Rep Hepatol 2017:3921027.
[10] EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus Infection. J Hepatol 2017;67:370–98.

Joan Llach
Marta Gómez-Hernando
Jordi Colmenero
Xavier Forns*
Liver Unit, Hospital Clínic, IDIBAPS and CIBEREHD, University of Barcelona, Barcelona, Spain

* Corresponding author.
E-mail address: xforns@clinic.cat (X. Forns)

31 May 2019

https://doi.org/10.1016/j.dld.2019.06.009

Early genetic testing of *STK11* is important for management and genetic counseling for Peutz–Jeghers syndrome

To the Editor,

Peutz–Jeghers syndrome (PJS) is a rare autosomal dominant inherited polyposis disorder (OMIM #175200), with an estimated incidence varying from 1/8300 to 1/280000 live births [1]. It is characterized by multiple gastrointestinal (GI) hamartomatous polyps, and mucocutaneous pigmentation, particularly on the vermilion border of lips. PJS patients have an increased lifetime risk of GI cancers and a wide spectrum of extra-GI malignancies [2,3]. More than 90% of PJS patients carry loss-of-function mutations at *serine-threonine kinase 11*(*STK11*, also named as *LKB1*, OMIM #602216), which is an important tumor suppressor gene controlling cell growth, division and apoptosis [4]. About 25% of PJS patients have de novo mutations of this gene [5]. PJS shows some clinical heterogeneity, such that pigmented lesions and gastrointestinal symptoms may not always be demonstrated in an affected individual [5]. Affected individuals, particularly those without family history of the condition, often pay insufficient attention if symptoms are not obvious, until they have to receive surgical treatment or develop cancer. Early diagnosis of this disease can be quite helpful for treatment and cancer surveillance and to improve life quality of PJS patients. Genetic testing for *STK11* gene is undoubtedly a promising and effective way.

Here, we report two unrelated Chinese PJS families, and identify a novel and probably *de novo* "pathogenic" mutation (c.1004_1005insT [p.Met335IlefsTer25]). The two families were unrelated and from Hubei province of China.

Family 1

A 12-year-old boy was referred for diagnosis for his growing mucocutaneous pigmentation. His father had similar symptoms at youth, but he did not pay attention until he suffered advanced colorectal cancer and then died of it at the age of 37 years. The boy had characteristic pigmentation on his lips, buccal mucosa and two hands. Pigmentation initially appeared on his lower lip at 6 months after birth, then increased with age and appeared on his fingers in recent months. Although the boy reported no GI symptoms (such as abdominal pain, diarrhea, and hematochezia), endoscopic examination found some polyps in the stomach and colon. The polyps were confirmed to be hamartomatous by pathological examination after endoscopic polypectomy and the boy was diagnosed with PJS. His father had mucocutaneous pigmentation and polyps, and died at the age of 37 due to colorectal cancer. His mother showed no features of PJS.

Family 2

A 30-year-old man was referred for further treatment of GI polys and for relevant genetic counseling. He had characteristic mucocutaneous freckling and reported years of intermittent abdominal pain. In 2005, he was diagnosed with polyposis and intestinal obstruction, and underwent surgical resection due to partial intestinal necrosis. Then, he received several surgical treatments because of multiple polyps on esophagus, stomach, small bowel and colon. The pathological examination revealed hamartomatous polyps. His mother, who had a similar history of intestinal obstruction at age 10 years, was also diagnosed with PJS based on pigmented lesions and GI hamartomatous polyps. Moreover, the patient and his affected mother had pigmentation initially at the age of 3 years. His 3-year-old daughter who presented two freckles in her left hand, and he wanted to know the risk of PJS for his daughter. No other family members demonstrated any PJS features.

Based on written informed consents, we collected blood samples from the probands of both families and their available family members. Genomic DNA was extracted using QIAamp DNA blood mini kit (Qiagen GmbH, Germany), and then subjected to polymerase chain reactions (PCR) to amplify the entire coding regions and splice boundaries of *STK11* gene (NP_000446.1, NM_000455.4, GRCh38.p7). The purified PCR products were analyzed by bidirectional sequencing using the ABI 3500 DNA sequencer (Applied Biosystems)

In family 1, a heterozygous 9-bp deletion, c.907_915delATCCGGCAG (p.Ile303_Gln305del), was detected in the boy (Fig. 1a and 1b, II: 1). The germline deletion was not detected in his unaffected mother (Fig. 1a and 1b, I: 2) and was speculated to be inherited from his affected father. The deletion was in exon 7 of *STK11* and could lead to loss of three amino acids in the kinase domain (Fig. 1e). This mutation has not been recorded in multiple population databases including Exome Aggregation Consortium (ExAC), 1000 Genomes Project, genomeAD and dbSNP. Integrative databases of MutationTaster and PROVEAN predicted that it was deleterious based on evidence including evolutionary conservation, protein features and structure. This mutation was also detected in a 14-year-old Thai girl in a previous report [6]. Taken together, c.907_915delATCCGGCAG (p.Ile303_Gln305del) is considered as a "likely pathogenic" mutation in *STK11* causing