

# Hepatocellular carcinoma after direct-acting antiviral therapy in kidney transplant recipients infected with hepatitis C virus

## Carcinoma hepatocelular después del tratamiento con antivirales de acción directa en pacientes trasplantados renales infectados con el virus de la hepatitis C

Dear Editor,

The success of direct-acting antivirals (DAA) against hepatitis C virus (HCV) was a major breakthrough in medicine. Many studies showed that DAA are safe and effective for chronic HCV infection treatment after kidney transplantation.<sup>1</sup> In 2018 KDIGO updated the Guidelines on chronic HCV in chronic kidney disease (CKD) including the recommendation that all infected kidney transplant recipients (KTR) should be evaluated for treatment.<sup>2</sup>

About KTR treated in our kidney transplantation unit<sup>3</sup> we would like to report two fatal cases.

The first was a 71-year-old male with IgA nephropathy with prior HCV infection (genotype 1b), who underwent kidney transplantation in 1991. In 2016 hepatic fibrosis (fibroscan F3) was documented and HCV treatment with ledipasvir/sofosbuvir was prescribed reaching sustained viral response (SVR) at 12 weeks. One year after therapy, elevation of alpha-fetoprotein (AFP) from 2.9 to 10.9 ng/ml (reference value <8.8 ng/ml) was noticed, despite undetectable HCV viral load. Hepatic ultrasound found no abnormalities but computed tomography showed extensive hepatic nodular involvement and partial portal vein thrombosis, suggestive of hepatocellular carcinoma (HCC). The patient died four months after HCC diagnosis, before treatment with sorafenib was started.

The second patient was a 72-year-old female with CKD due to chronic pyelonephritis who underwent renal transplantation in 2003. She had prior chronic HCV infection (genotype 1a) and had documented hepatic cirrhosis (fibrosan F4). Treatment with sofosbuvir/ledipasvir/ribavirin was given 13 years after transplantation, reaching SVR at 24 weeks. Eleven months later, AFP increased (7.2–2864 ng/ml). Despite normal hepatic ultrasound, magnetic resonance imaging showed a nodular lesion compatible with HCC. The lesion was successfully embolized. Ten months later, bone metastasis was evident as she suffered a fracture on her left hip. Bone biopsy confirmed metastatic HCC. Although HCV viral load remained undetectable, the patient died 14 months after the diagnosis.

Even after HCV eradication by DAA, the risk of progression to HCC remains a threat. As illustrated in these two cases, the suspicion was raised by an increasingly AFP despite an unsuspected ultrasound.

In patients with chronic HCV infection and cirrhosis, the risk of developing HCC remains uncertain. However this risk is significantly reduced compared to untreated patients or in the ones who did not achieve SVR.<sup>4</sup> The European Association for the Study of the Liver recommends that patients with advanced fibrosis or cirrhosis with SVR should undergo surveillance for HCC every 6 months by means of ultrasound.<sup>5</sup> However, in these two KTR cases, ultrasound was ineffective for detection of HCC, which occurred less than one year after apparently successful DAA therapy.

The purpose of reporting these two cases is fourfold: (1) to alert for the need to fully evaluate patients who display an increase of AFP levels; (2) ultrasound may not be a sensitive method to HCC diagnosis; (3) to raise the possibility that immunosuppression may eventually increase the oncogenic potential of previous HCV infection; (4) as HCV infection lasted for many years and HCC developed shortly after DAA a causal relation cannot be discarded.

### Conflicts of interest

The authors disclose no conflicts of interest.

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Rita Calça<sup>a,\*</sup>, Cristina Jorge<sup>a</sup>, Luís Lebre<sup>b</sup>, Eunice Cacheira<sup>a</sup>, Sara Querido<sup>a</sup>, Célia Nascimento<sup>a</sup>, Teresa Adragão<sup>a</sup>, Margarida Bruges<sup>a</sup>, André Weigert<sup>a</sup>, Domingos Machado<sup>a</sup>

<sup>a</sup> Department of Nephrology, Hospital Santa Cruz – Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal

<sup>b</sup> Department of Gastroenterology, Hospital Egas Moniz – Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal

\* Corresponding author.

E-mail address: [arrcalca@gmail.com](mailto:arrcalca@gmail.com) (R. Calça).

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## Immunoglobulin A vasculitis in a patient with neurofibromatosis type 1

### Vasculitis por inmunoglobulina A en un paciente con neurofibromatosis tipo 1

Dear Editor,

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder that affects multiple organ systems.<sup>1</sup> It can be diagnosed if a patient presents with two or more of the following features: six or more café-au-lait macules of larger than 5 mm in diameter before puberty or larger than 1.5 mm in diameter after puberty, axillary or inguinal skinfold freckling, two or more dermal neurofibromas or one plexiform neurofibroma, two or more iris hamartomas, an optic pathway glioma, a distinctive long bone dysplasia involving the sphenoid wing or thinning of the long bone cortex with or without pseudarthrosis, and a first-degree relative with NF1.<sup>2</sup> Neurofibromas, one of the main clinical features, usually present as discrete nodules or pedunculated masses, but cannot be presented as vasculitic skin purpura.<sup>3</sup> Here, we report a female patient with NF1 who demonstrated vasculitic skin rash.

A 56-year-old Japanese woman with neurofibromatosis type 1 presented with new onset of microscopic hematuria, abdominal pain, and arthralgia. Her past medical history included the left limb amputation due to a traffic accident and malignant peripheral nerve sheath tumours. She had no previous history of renal disease and denied any use of tobacco or alcohol. Upon physical examination, her respiratory rate was 14 breaths per minute, heart rate was 106 beats per minute, blood pressure was 137/85 mmHg, and body temperature was 36.7°C. Notable examination findings included generalized neurofibromas, palpable purpura on the right leg (Fig. 1), and a slight tenderness at the epigastric area. The musculoskeletal examination showed mild pain in the bilateral elbow joints. Urinalysis showed >100 erythrocytes per high-power field and

0.54 g/gCr of proteinuria. The kidney function was normal (blood urea nitrogen level, 15.6 mg/dL; serum creatinine level, 0.44 mg/dL). Renal biopsy revealed mild mesangial proliferation with granular immunoglobulin A (IgA) deposition, and skin biopsy showed leukocytoclastic vasculitis with IgA deposition. The diagnosis of IgA vasculitis (IgAV) was made based on the European League Against Rheumatism, the Paediatric Rheumatology International Trials Organizations, and the Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) classification criteria.<sup>4</sup>

IgAV is a small-vessel vasculitis, involving the skin, joints, and kidney. According to the EULAR/PRINTO/PRES classification criteria, the diagnosis of IgAV is confirmed by the presence of purpura and one of the following clinical manifestations: abdominal pain, arthralgia, renal insufficiency, and leukocytoclastic vasculitis with predominant IgA deposits.<sup>4</sup> Proteinuria, hematuria, or renal insufficiency are present in 70–80% of adult patients with IgAV.<sup>5</sup> There is no specific treatment for IgAV because it generally resolves spontaneously; however, renin-angiotensin system inhibitors and corticosteroid therapy are recommended to reduce proteinuria and maintain kidney function in moderate and severe cases.<sup>6</sup>

By contrast, neurofibromatosis type 1, an autosomal dominant disorder caused by germline mutations in the NF1 tumour suppressor gene, can manifest progressive multiple organ dysfunctions in the skin, bones, eyes, and neuropsychiatric system.<sup>1</sup> Neurofibromas and café-au-lait macules are the main skin features, whereas, palpable purpura is not.<sup>3</sup> Regular assessment of neurofibromas (owing to the increased risk of malignant peripheral nerve sheath tumours), vitamin D supplementation (owing to the increased risk of osteoporosis), blood pressure monitoring (owing to the increased risk