Clinics and Research in Hepatology and Gastroenterology (2016) xxx, xxx.e1—xxx.e4

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

CASE REPORT

# Paraneoplastic fibrillary glomerulonephritis associated with intrahepatic cholangiocarcinoma: When diagnosis of a rare kidney disease leads to successful hepatic cancer treatment

**Gabrielle Normand[a,*], Anne Jolivot[a], Maud Rabeyrin[b], Valérie Hervieu[b], Pierre-Jean Valette[c], Jean-Yves Scoazec[d], Jean-Michel Gougon[e], Laurent Juillard[a], Jérôme Dumortier[f]**

[a] *Service de néphrologie clinique, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France*
[b] *Service d'anatomopathologie, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France*
[c] *Service d'anatomopathologie, CHU de Poitiers, Poitiers, France*
[d] *Service de radiologie, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France*
[e] *Service de radiologie, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France*
[f] *Service d'hépato-gastro-entérologie, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France*

**Summary** A 50-year-old man presented with nephrotic syndrome. Electron microscopy analysis of a kidney biopsy specimen showed fibrillary glomerulonephritis, a rare glomerular disease, while histological analysis of a liver tumor biopsy confirmed an intrahepatic cholangiocarcinoma. The paraneoplastic nature of fibrillary glomerulonephritis is debated but after curative treatment of the hepatic nodule, remission of nephrotic syndrome was confirmed at 6-, 12- and 24-months follow-up. To our knowledge, this is the first description of a paraneoplastic fibrillary glomerulonephritis associated with a cholangiocarcinoma, supported by complete remission achieved following cancer treatment.


*Abbreviations:* ALT, alanine transaminase; ANCA, anti-neutrophil cytoplasmic antibodies; Anti PLA2R antibodies, anti phospholipase A2 receptor antibodies; AST, aspartate transaminase; CCa, cholangiocarcinoma; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; FGN, fibrillary glomerulonephritis; RAS, renin—angiotensin system.

* Corresponding author at: Service de Néphrologie, Pavillon P, 5, Place d'Arsonval, Hôpital Edouard Herriot, 69003 Lyon, France.
*E-mail address:* gl.normand@hotmail.fr (G. Normand).

http://dx.doi.org/10.1016/j.clinre.2016.07.002
2210-7401/

## Introduction

Fibrillary glomerulonephritis (FGN) is a rare cause of glomerular diseases [1,2]. First description of Congo Red negative fibrillar deposits in the mesangium or glomerular basement membrane by Rosenmann and Eliakim in 1977, led to the term of FGN in 1987 by Alpers et al. [3]. Authors differentiate immunotactoid glomerulopathy and FGN depending on fibrils size, orientation, and arrangement [4,5]. FGN is characterized by mesangial and/or capillary wall deposits of randomly arranged fibrils, ranging from 10 to 30 nm in external diameter, stained with antisera to Ig heavy and light chains. Diagnosis is based on electron microscopy while light microscopy findings are often unspecific and variable [3]. Immunofluorescence microscopy is positive for IgG (100%), C3, and both kappa and lambda (polyclonal) light chains [2,6].

FGN was initially thought to be idiopathic, but recent case series showed its frequent association with malignancy, monoclonal gammopathy, hepatitis C, and autoimmune diseases [2,6] with up to 23% of patients developing cancers 10 years before to 15 years after FGN diagnosis in the study of Nasr et al. [2]. We report here the first description of a paraneoplastic FGN associated with an intrahepatic cholangiocarcinoma (CCa), supported by complete remission achieved following curative liver cancer treatment.

## Case report

A 50-year-old man was referred to Edouard Herriot Hospital hepatology unit (Lyon, France) in September 2013, because of ALT and AST flare over 2 folds the normal upper limit, and severe hypoalbuminemia (1.7 g/dL). He had a history of chronic liver disease of unknown etiology, complicated by esophageal varices rupture leading to a surgical portosystemic shunt in 1982, at the age of 19. He also had untreated hypertension since he was 19 years old. He worked as a dental surgeon. Physical examination revealed acute lower limbs and face edema, with uncontrolled hypertension at 170/110 mmHg. Neurological, dermatological and rheumatologic examinations were normal. Complete blood analysis showed creatininemia in the normal range (0.96 mg/dL — estimated Glomerular Filtration Rate (eGFR) = 96 ml/min using CKD-EPI formula) and there was no inflammatory syndrome (CRP lower than 10 mg/L). The 24 h-proteinuria was within the nephrotic range at 3 g/day and urinary sediment showed aseptic leukocyturia and microscopic hematuria.

Serological tests for viral infections (hepatitis B, C, HIV) were negative. Anti-nuclear, ANCA, anti PLA-2R, and anti-glomerular basement membrane antibodies were negative. There was no cryoglobulinemia and complement was normal. Serum protein electrophoresis showed hypoalbuminemia with no peak; 24 h-proteinuria was lowered to 0.74 g/day. Because of professional exposure to dental amalgams, urine and blood were tested for silica and mercury, which were in the normal range. Liver tests showed no cholestasis and normal bilirubin. Alpha-fetoprotein ($\alpha$FP) was within the normal range. Ultrasonography of the abdomen showed a permeable porto-systemic shunt with no liver nodule. Kidney measurement showed normal size and there was no dilation of calyces. The patient underwent a kidney biopsy after introduction of RAS inhibitors for 2 weeks. Light microscopy study of a kidney biopsy showed 41 glomeruli with no sclerotic glomerulus. Glomerular pattern was a diffuse proliferative glomerulonephritis associated with chronic vascular lesions, with IgG, IgM, C1q, C3 and Kappa and Lambda light chains deposits. The material was Congo red negative. Electron microscopy examination led to the diagnosis of FGN with randomly arranged fibrillary deposits of 12—20 nm in external diameter without duplication of the glomerular basement membrane (Fig. 1).

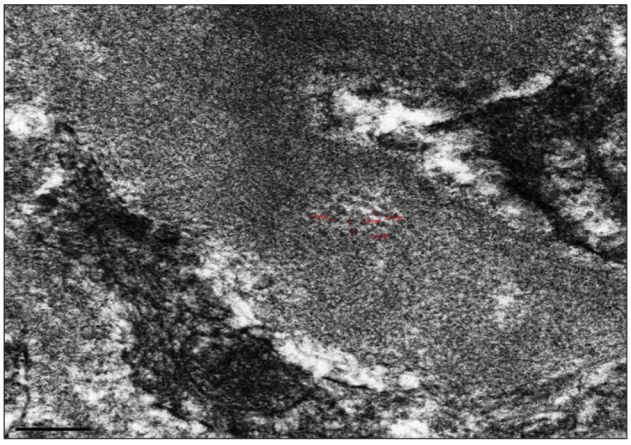

**Figure 1** Fibrillary glomerulonephritis. Electron microscopy photomicrograph showing mesangial deposits, composed of randomly arranged fibrils 10—20 nm in diameter (100,000×).

Bone marrow aspirate examination showed no plasma cell proliferation but bone marrow edematous degeneration, suspected to be related to severe hypoalbuminemia and denutrition. A total body CT scan showed a small hypervascular tumor (2 cm diameter) in the right liver lobe, without dilatation of peripheral bile ducts. On MRI T1 and T2-weighted images, nodule appeared hyperintense; T1 contrast injection (Gadolinium) showed mild hypervascularization of this mass (Fig. 2). A liver biopsy of the nodule and also non-tumoral adjacent liver was performed. Histological analysis of the biopsy disclosed a tubular adenocarcinoma made of eosinophilic tumor cells with small cytoplasm and ovoid or round nuclei with mild atypia. Mucin production was absent. Tumor structures were embedded in an abundant fibrous stroma. At immunohistochemical examination, tumor cells expressed cytokeratins 7 and 19 and NCAM; they did not express the hepatocellular makers HepPar-1, Glypican-3 and arginase-1. CD10 and CEA exhibited an apical pattern of expression. There was no expression of stem cell markers (CD117). The tumor was therefore classified as intrahepatic cholangiocarcinoma. The peritumoral liver tissue showed architectural changes suggestive of chronic vascular disease with regenerative nodular hyperplasia.

Percutaneous microwave ablation of the lesion allowed a complete regression of the nodule at the 2-months follow up, confirmed at 6-, 12- and 24-months follow-up while remission of proteinuria was achieved at the 6-months follow up. Liver tests were normalized while renal function was slightly deteriorated with a creatininemia up to 1.07 g/dL (eGFR = 80 ml/min with the CKD-EPI formula).

Please cite this article in press as: Normand G, et al. Paraneoplastic fibrillary glomerulonephritis associated with intrahepatic cholangiocarcinoma: When diagnosis of a rare kidney disease leads to successful hepatic cancer treatment. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.07.002