



LETTER TO THE EDITOR

Serum levels of carbohydrate antigen 19-9 do not systematically increase in case of liver cyst infection in patients with autosomal dominant polycystic kidney disease

Marie F. Neuville^{1,2}, Jean-Marie Krzesinski^{1,2} and François Jouret^{1,2}

¹Division of Nephrology, Department of Internal Medicine, University of Liège Hospital, Liège, Belgium and ²Groupe Interdisciplinaire de Génomique et Protéomique Appliquée, Cardiovascular Sciences, University of Liège, Liège, Belgium

Correspondence to: François Jouret; E-mail: francois.jouret@chuliege.be

Liver cyst infection (LCI) is a rare but life-threatening complication of autosomal dominant polycystic kidney disease (ADPKD) [1]. Its diagnosis remains problematic given the lack of specific and sensitive symptoms and signs. In 2009, Sallée et al. [2] proposed diagnostic criteria: 3-day fever >38.5°C, liver tenderness, plasma C-reactive protein (CRP) levels >50 mg/L and no evidence for cyst haemorrhage on computed tomography (CT). ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) has proved useful in LCI diagnosis [3, 4]. In 2010, Kanaan et al. [5] reported on an elevation of serum levels of carbohydrate antigen 19-9 (CA19-9) (compared with individual baseline level) in three kidney transplant recipients (KTRs) with ADPKD and bilateral nephrectomy who presented with LCI. These observations suggested a potential utility of CA19-9 as a diagnostic biomarker of LCI in ADPKD patients.

CA19-9 is classically used as a biomarker for biliopancreatic malignancies [6]. Serum CA19-9 may also increase in other types of cancer as well as in non-malignant conditions [7]. Interestingly, serum levels of CA19-9 are constitutively high in patients with polycystic liver diseases, including autosomal dominant polycystic liver disease and ADPKD, due to a leakage from cysts into lymphatic or capillary vessels [8, 9]. Of the ADPKD patients, 19–44% present with elevated basal serum levels of CA19-9 [5, 7, 9], with an adapted upper threshold of 106 kU/L (corresponding to the 90th percentile) [5]. Serum levels of gamma-glutamyltransferase and the volume of liver cysts

are independent predictors for basal serum CA19-9 levels [9]. Serum CA19-9 concentrations are not influenced by the glomerular filtration rate [10]. The impact of kidney transplantation and/or immunosuppressive drugs on CA19-9 levels has not been studied thus far.

In this study we retrospectively evaluated the clinical relevance of serum CA19-9 levels in the diagnosis of LCI in ADPKD patients (Table 1). Our work was approved by the Commission of Biomedical Ethics of the University of Liège Hospital, Liège, Belgium. Using our systematic computerized billing database, we identified seven episodes of LCI in five different patients in whom serum CA19-9 levels had been measured at the time of LCI [using the monoclonal antibody #1116-NS-19-9 on a Cobas e602 (Roche, Basel, Switzerland)]. Five episodes met the clinicobiological diagnostic criteria and six showed a typical accumulation of ¹⁸F-FDG around the infected cysts detected by PET/CT imaging (n=6) done after a median of 7 days [interquartile range (IQR) 4–13] post-admission. The median age of the cohort reached 73 years (IQR 54–79). The female:male ratio was 4:3. The median body mass index was 26.4 kg/m² (IQR 22.8–28.3). Six LCI episodes occurred in KTRs. Blood analyses detected the causative germ in six cases: *Klebsiella pneumoniae* (n=3), *Escherichia coli* (n=2) and *Acinetobacter species* (n=1). All urinalyses were negative. The median CA19-9 level at the time of LCI was 29.7 kU/L (IQR 16.2–81.5), with four episodes within the normal range (<34 kU/L). Baseline serum CA19-9 levels were

Received: 25.7.2019; Editorial decision: 7.8.2019

© The Author(s) 2019. Published by Oxford University Press on behalf of ERA-EDTA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Table 1. Clinical and biological features of our cohort

Patient	Gender	Age	BMI	KTR	Pain	Fever	CRP	CT	PET/CT	CA 19-9	bCA 19-9	ΔCA 19-9	Blood culture
1	F	54	22.8	–	+	+	454	–	ND	57.2	45.7	11.5	–
2	F	77	28.3	+	–	–	132	–	+	81.5	79.3	2.2	<i>Acinetobacter species</i>
3	M	73	26.7	+	–	–	283	–	+	61.8	39.6	22.2	<i>Klebsiella pneumoniae</i>
		73	26	+	+	+	127	–	+	29.7	39.6	–9.9	<i>Escherichia coli</i>
4	F	78	26.4	+	+	+	109	–	+	16.2	28.7	–12.5	<i>Klebsiella pneumoniae</i>
		79	26.8	+	+	+	154	–	+	19.5	28.7	–9.2	<i>Klebsiella pneumoniae</i>
5	M	67	25	+	+	+	177	–	+	29.3	ND	–	<i>Escherichia coli</i>

Age, age (years) at the time of LCI; BMI, body mass index (kg/m²); Pain, liver tenderness; Fever, temperature $\geq 38.5^{\circ}\text{C}$ for 3 days; CRP, peak value of plasma CRP within 72 h upon hospital admission (mg/L); CA 19-9, serum levels of CA 19-9 at the time of LCI (kU/L; normal range ≤ 34 kU/L); bCA 19-9, baseline serum levels of CA 19-9; ΔCA 19-9, difference between serum levels of CA 19-9 at the time of LCI versus baseline; Blood culture, identification of the causative germ in blood; M, male; F, female; ND, not done; PET/CT +, ¹⁸F PET imaging suggestive of LCI; CT –, abdominal CT showing no cyst haemorrhage or other cause of fever.

available in four patients, i.e. six episodes. The median CA19-9 level at baseline, i.e. sampled at a distance from any biliopancreatic digestive pathologies, reached 39.5 kU/L (IQR 28.7–79.3), with two cases within the normal range. Among these six LCIs, three cases (50%) showed decreased serum levels of CA19-9 at the time of LCI compared with baseline values (Table 1).

Despite the limited number of patients/episodes, our retrospective observations show that the serum levels of CA19-9—in absolute values or in deltas relative to individual baseline values—do not systematically increase in case of LCI in ADPKD patients. Given the cost of CA19-9 dosage and its large inter- and intra-individual variability in ADPKD patients at baseline and in case of LCI, the clinical relevance of measuring serum levels of CA19-9 in ADPKD patients with a suspected LCI is questioned.

CONFLICT OF INTEREST STATEMENT

None declared. These observations have been presented (poster) at the ERA-EDTA meeting in Budapest. They have been recently accepted as an oral presentation at the European Society for Organ Transplantation meeting in Copenhagen, Denmark.

REFERENCES

- Jouret F, Lhommel R, Devuyst O et al. Diagnosis of cyst infection in patients with autosomal dominant polycystic kidney disease: attributes and limitations of the current modalities. *Nephrol Dial Transplant* 2012; 27: 3746–3751
- Sallée M, Rafat C, Zahar J-R et al. Cyst infections in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 1183–1189
- Jouret F, Lhommel R, Beguin C et al. Positron-emission computed tomography in cyst infection diagnosis in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2011; 6: 1644–1650
- Neuville M, Hustinx R, Jacques J et al. Diagnostic algorithm in the management of acute febrile abdomen in patients with autosomal dominant polycystic kidney disease. *PLoS One* 2016; 11: e0161277
- Kanaan N, Goffin E, Pirson Y et al. Carbohydrate antigen 19-9 as a diagnostic marker for hepatic cyst infection in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 2010; 55: 916–922
- Locker GY, Hamilton S, Harris J et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006; 24: 5313–5327
- Fliszkiewicz M, Niemczyk M, Kulesza A et al. Carbohydrate antigen 19-9 level in patients with autosomal dominant polycystic kidney disease. *Transplant Proc* 2018; 50: 1631–1633
- Waanders E, van Keimpema L, Brouwer JT et al. Carbohydrate antigen 19-9 is extremely elevated in polycystic liver disease. *Liver Int* 2009; 29: 1389–1395
- Fukasawa H, Kaneko M, Niwa H et al. Carbohydrate antigen 19-9 is significantly elevated in autosomal dominant polycystic kidney disease. *Nephrology* 2018; 23: 210–216
- Mikkelsen G, Hov GG. Reference limits for chromogranin A, CYFRA 21-1, CA 125, CA 19-9 and carcinoembryonic antigen in patients with chronic kidney disease. *Int J Biol Markers* 2017; 32: e461–e466