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Original Article

Solid renal tumours of collecting duct origin in patients on chronic lithium therapy

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Abstract

Background. Lithium (Li) is an invaluable drug for the treatment of bipolar disorder. Long-term Li use is associated with renal complications including the formation of uncomplicated renal cysts caused by proliferation and expansion of collecting duct (CD) cells. We report six patients with complicated renal cysts in the context of Li nephropathy.

Methods. Over a time period of 15 years, we have identified six patients with one or more solid renal tumours in our population of approximately 50 patients with chronic Li nephropathy. In this study we describe the clinical and pathological characteristics of these Li-related tumours.

Results. All patients were on Li therapy for over 10 years and suffered from varying degrees of Li nephropathy. The tumours were all of CD origin and comprised both oncocytomas and collecting duct carcinomas. The CD carcinomas differed from the very rare "classical" CD cell carcinomas in histological appearance, multifocal presentation and non-aggressive clinical behaviour

Conclusions. The increased incidence of CD derived tumours and atypical presentation of CD cell carcinomas in patients with chronic Li nephropathy suggests that Li predisposes to the development of these tumours. We hypothesize that prolonged stimulation of CD cell proliferation and expansion by Li not only causes cyst formation, but can eventually induce the formation of adenomas and carcinomas. Increased awareness of a possible relationship between chronic Li therapy and renal neoplasms, will enhance the knowledge on epidemiology, clinical behavior and optimal therapy for the Li-related renal neoplasms.

Keywords: cancer; cyst; lithium

Introduction

Lithium (Li) is an invaluable drug for the treatment of bipolar disorder, with 1:500 people using Li in Western societies. Chronic Li use is associated with several renal complications. Renal diabetes insipidus occurs in up to 40% of the patients and ∼20% develop chronic tubulointerstitial nephritis that is associated with slowly progressive renal failure. A third aspect of chronic renal Li toxicity, acquired polycystic kidney disease, has received little attention to date. Animal experiments have shown that Li induces a proliferative response in the kidneys, specifically in the CD, causing tubular dilation and cyst formation [1]. In patients with lithium nephropathy, abundant renal cysts are found using magnetic resonance imaging (MRI) and ultrasound [2]. In addition, dilation of CD and cyst formation are distinguishing features in kidney biopsies of these patients [3]. Until now, however, only uncomplicated renal cysts have been attributed to chronic Li use. Here, we report for the first time that complicated solid renal masses can occur in the context of Li nephropathy and show that these tumours are of CD origin.

Cases

Over a time period of 15 years, we have identified six patients with one or more solid renal tumours in our population of ∼50 patients with chronic Li nephropathy (Table 1). All patients were on Li therapy for more than 10 years and suffered from varying degrees of chronic renal failure and renal diabetes insipidus. The renal tumours were incidental findings during work up for renal dysfunction (Patients 1, 4 and 5) or upon analysis of non-specific abdominal complaints (Patients 2, 3 and 6). The abdominal scans made to exclude regional metastases showed multiple uncomplicated renal cysts in all patients (Figure 1). In addition, a complicated cyst was found in the contralateral kidney in one patient (Patient 4).

Histological evaluation demonstrated that all tumours were of collecting duct (CD) origin (Table 2). In three

Table 1. Patient characteristics

Patient no.	Age (years)	Sex	Li use (years)	Plasma creatinine [μmol/L (mg/dL)]	Radiological findings	Intervention	Lithium	Follow-up
1	69	M	17	444 (5.0)	Solid tumour L kidney (4.5 cm)	Nephrectomy, haemodialysis	Continued	1 year, died of unrelated cause
2	71	F	30	125 (1.4)	Solid tumour R kidney (4.0 cm)	Partial nephrectomy	Continued	5 years, died of unrelated cause
3	59	M	12	133 (1.5)	Solid tumour R kidney (3.0 cm)	Nephrectomy	Continued	4 years, no recurrence
4	70	M	30	765 (8.7)	Solid tumour L kidney (3.0 cm), complicated cyst R kidney	Biopsy tumour L kidney, radiological follow-up	Stopped	2 years, no growth of lesions
5	61	M	15	135 (1.5)	Solid tumour L kidney (3.5 cm)	Biopsy, awaiting surgery	Continued	4 months, no tumour growth
6	65	F	41	135 (1.5)	Solid tumour R Kidney (2.6 cm)	Biopsy, radiological follow-up	Continued	4 months

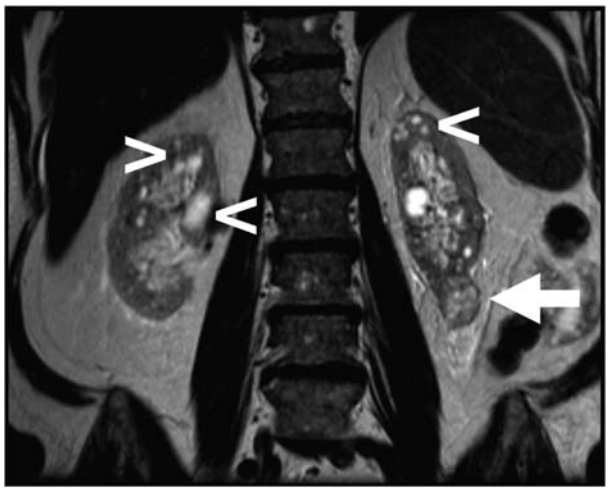

Fig. 1. Typical MRI of a CD tumour in a patient on chronic lithium therapy. A large tumour can be seen in lower pole of the left kidney (arrow). In addition, numerous renal cysts are present in both kidneys (open arrows).

Table 2. Tumour characteristics

Patient no.	Tumour, no.	Histology	CK 19	Vimentin	Other markers present
1	1	CD carcinoma	+	+	CK8, 18 (CAM5.2), KL1; CK HMW; EMA
2	1	Oncocytoma			
	2	CD carcinoma	+	+	CK8, 18 (CAM5.2); CD15
3	1	CD carcinoma	+	+	CK8, 18 (CAM5.2); CK HMW; CD15
4	1	Oncocytoma			
5	1	CD carcinoma	+	+	EMA; CD15; CK HMW; CK7; CD10; E-cadherin
6	1	Oncocytoma			

CK, cytokeratin; EMA, epithelial membrane antigen; CK HMW, high-molecular-weight cytokeratin.

patients, histology and immunohistochemistry showed the presence of a CD cell carcinoma (Patients 1, 3 and 5; Figure 2). In the three other patients, the tumours had the typical histological appearance of a renal oncocytoma (Figure 3). In the resection edge of the partial nephrectomy specimen of one of the latter patients (Patient 2), a CD cell carcinoma was found that had not been recognized on the computed tomographic (CT) scan.

The renal tissue surrounding the tumours showed dilation of the CD, abundant cyst formation and diffuse interstitial fibrosis and lymphocytic infiltration. In Patients 2 and 3, not only dilated CD and cysts were seen, but also papillary projections of the tubular epithelium into the lumen of several CDs or cysts (Figure 4).

None of the patients had distant metastases on CT scanning and therapy varied from watchful waiting because of considerable comorbidity (Patients 4 and 6) to partial or complete unilateral nephrectomy (Table 1). Patient 1 became dialysis-dependent after nephrectomy. None of the patients died from renal malignancy, despite incomplete removal of a CD cell carcinoma (Patient 2), extension of the tumour into the perirenal fat (Patient 3), the presence of a contralateral complicated renal cyst (Patient 4) or the development of two complicated cysts in the contralateral kidney after unilateral nephrectomy (Patient 1). All patients except for one continued the use of Li because of inadequate psychiatric control on alternative pharmacotherapy.

Discussion

We report six patients who developed solid renal lesions of CD origin in the context of chronic Li nephropathy. The detection of these tumours in six patients among ~50 patients with chronic Li nephropathy known at our department suggests that Li use predisposes to the development of CD neoplasms. Reports of renal neoplasms in patients on chronic Li therapy are very rare, and the connection with the use of Li was not made specifically. In a series of 24 renal biopsies in patients with Li nephropathy, Markowitz *et al.* [3] reported two tumours, of which one was a CD cell carcinoma. Because of limited immunohistochemical evaluation, the origin of the other tumour remained unresolved. In addition, in three unselected histology specimens of humans on Li therapy, Kjaersgaard *et al.* [4] described features of typical Li nephropathy in a kidney removed because of an unclassified renal carcinoma.

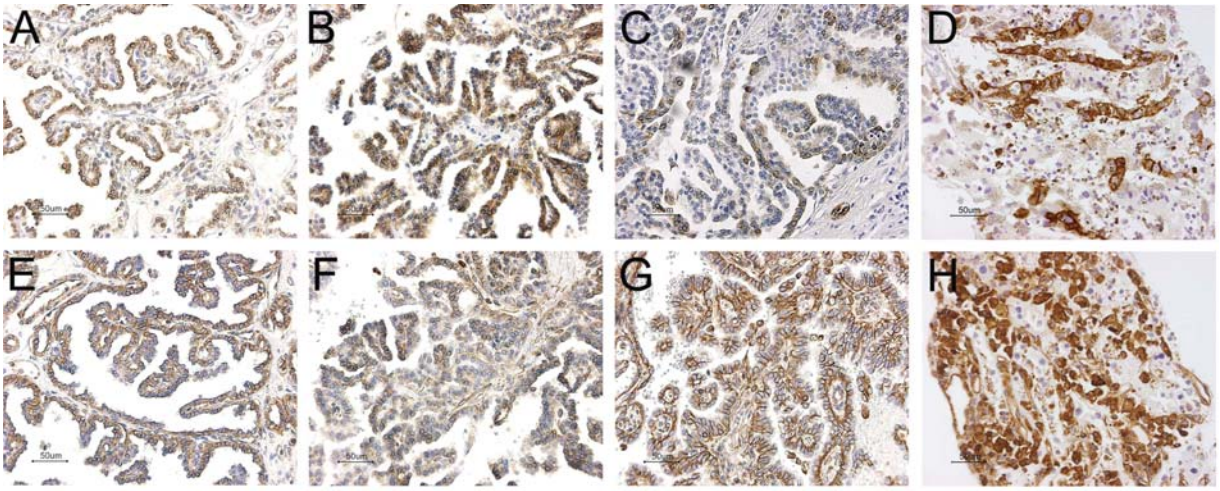

Fig. 2. Immunohistochemistry of the CD cell carcinomas. Cytokeratin 19 (**A–D**) and vimentin (**E–H**) staining of CD carcinomas (brown). A, E: Case 1; B, F: Case 2; C, G: Case 3, D, H: Case 5. Bar represents 50 μm.

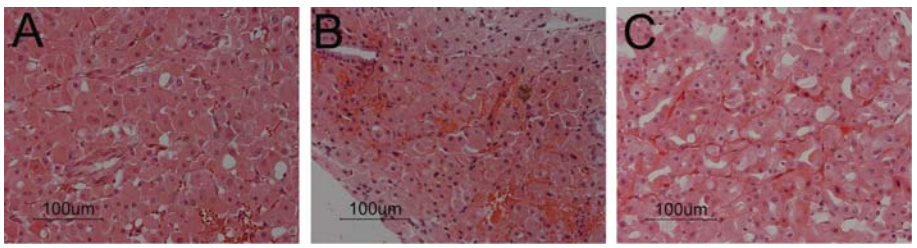

Fig. 3. HE staining of renal oncocytomas. Large well-differentiated cells can be seen with eosinophilic granular cytoplasm in Cases 2, 4 and 6 (**A–C**).

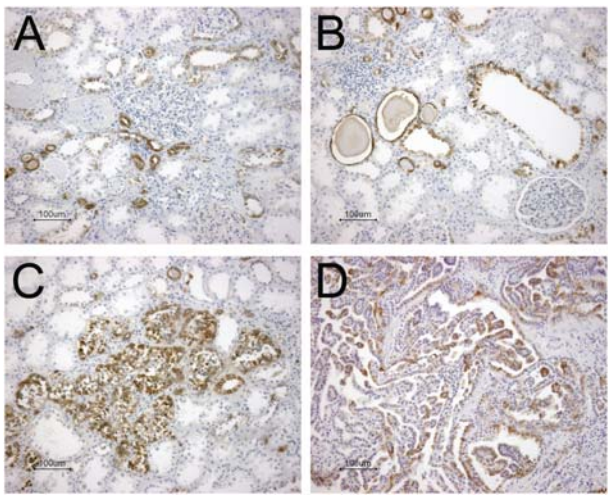

Fig. 4. Cytokeratin 19 staining of the different parts of the same kidney (Case 3). (**A**) Normal renal tissue with cytokeratin 19 staining of the CD. (**B**) Cyst formation in cytokeratin 19-positive CD. (**C**) Cytokeratin 19-positive papillary structures within the cystic dilated CD. (**D**) Cytokeratin 19 staining of CD tumour. Bar represents 100 μm.

CD cell carcinomas are derived from principal cells in the CD. Interestingly, Li can reach very high concentrations in the CD, exceeding that in plasma by 20- to 40-fold [5]. The principal cells in the CD express the epithelial sodium channel apically which has a considerable Li permeability, causing high intracellular Li concentrations [6]. Intracellular Li can inhibit the enzyme glycogen synthase kinase 3 beta (GSK-3β) by phosphorylation. In agreement with this, cells lining the renal microcysts in patients on chronic Li therapy contain phosphorylated GSK-3β [4]. GSK-3β regulates the breakdown of β-catenin; consequently, GSK-3β inhibition increases the availability of β-catenin. Indeed, it has been shown that Li increases β-catenin availability in principal cells [7]. Increased availability of β-catenin in tubular cells is associated with both increased cell proliferation and cyst formation [8]. We hypothesize that prolonged stimulation of principal cell proliferation by Li not only causes cyst formation, but can also eventually induce adenomas and carcinomas.

The CD cell carcinomas associated with Li use in our patients differ from the 'classical' CD cell carcinomas. The latter tumours are rare, with an incidence of less than 2 per 1 000 000 person years [9]. In contrast, the four CD cell carcinomas in our population of ∼50 patients with Li nephropathy suggest a much higher incidence in patients with Li nephropathy. Histologically, the Li-induced tumours show a more pronounced papillary growth, whereas the tumour cells do not always retain the hobnail appearance, typical of classical CD cell carcinomas. In addition, the lesions found in patients with Li nephropathy tend to occur multifocally (Patients 1, 2 and 4), which is not surprising in view of the widespread Li-induced proliferation in CD throughout both kidneys. Both multifocality and growth pattern are atypical for classical CD carcinomas. Finally, the clinical behaviour of the Li-associated CD cell tumours

appears to be more benign than that of classical CD cell carcinomas. The latter are aggressive tumours with 80% lymph node metastases at presentation and a median survival of only 22 months [10]. In contrast, the tumours in our patients were subclinical, without metastases or recurrences during follow-up.

The pathophysiology of lithium-related oncocytomas exposure is less straight forward. Oncocytomas are mostly benign lesions comprising 3–7% of all renal tumours. Renal oncocytomas are derived from intercalated cells, which do not possess an entry mechanism for Li. It therefore appears unlikely that Li directly enhances the proliferation of intercalated cells. However, animal experiments have shown that Li treatment not only induces the proliferation of principal cells, but also causes an increase in the number of intercalated cells, possibly resulting from proliferation and differentiation of progenitor cells or the conversion of principal cells into intercalated cells [1]. Similar mechanisms may be involved in the development of oncocytomas in patients on Li therapy.

Our data raise the question of whether patients with chronic Li nephropathy should be screened for renal cysts and which strategy should be applied in case a complex cyst or solid tumour is found. A subset of these tumours are oncocytomas, which are often slow-growing benign neoplasms that require only surgical intervention in the case of rapid growth or a large tumour volume [11]. Although the remainder of the Li-induced tumours are classified as CD cell carcinomas, these tumours appear to differ from 'classical' CD cell carcinomas, specifically with respect to their clinical behaviour. The benign clinical behaviour challenges the indication for surgery, which results in loss of renal mass in patients with already compromised renal function. The observation of multifocal Li-related renal masses in our cases makes the decision to perform surgery even more difficult. Until more information is obtained on the incidence and natural history of Li-related proliferative renal disease, we do not suggest radiological screening in patients with Li nephropathy. In the case of a renal mass found incidentally in a patient on chronic Li therapy, we would suggest a biopsy. If an oncocytoma is found, careful radiological follow-up would be sufficient. If a CD cell carcinoma is found, the same strategy could be considered in view of the benign clinical behaviour of the tumours in our cases. However, treatment should be individualized and surgical removal may be preferred if a biopsy is technically not feasible, the tumour grows rapidly or removal of the tumour would imply only minimal loss of renal mass. Although Li is often an indispensable drug in patients with psychiatric disease, we suggest that the use of lithium be stopped in patients with progressive cystic kidney disease or a complex renal cyst. This suggestion is supported by the observation that most patients have slowly progressive renal failure, which in itself forms an indication to stop the use of Li. Increased awareness of a possible relationship between chronic Li therapy and renal neoplasms will enhance the knowledge on epidemiology, clinical behaviour and optimal therapy for the Li-related renal neoplasms.

Conflict of interest statement. None declared.

References

1. Christensen BM, Kim YH, Kwon TH *et al*. Lithium treatment induces a marked proliferation of primarily principal cells in rat kidney inner medullary collecting duct. *Am J Physiol Renal Physiol* 2006; 291: F39–F48
2. Farres MT, Ronco P, Saadoun D *et al*. Chronic lithium nephropathy: MR imaging for diagnosis. *Radiology* 2003; 229: 570–574
3. Markowitz GS, Radhakrishnan J, Kambham N *et al*. Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. *J Am Soc Nephrol* 2000; 11: 1439–1448
4. Kjaersgaard G, Madsen K, Marcussen N *et al*. Tissue injury after lithium treatment in human and rat postnatal kidney involves glycogen synthase kinase 3beta-positive epithelium. *Am J Physiol Renal Physiol* 2012; 302: F455–F465
5. Birch NJ, Hullin RP. Lithium and the kidney. *Br Med J* 1980; 280: 1148–1149
6. Kortenoeven ML, Li Y, Shaw S *et al*. Amiloride blocks lithium entry through the sodium channel thereby attenuating the resultant nephrogenic diabetes insipidus. *Kidney Int* 2009; 76: 44–53
7. Nielsen J, Hoffert JD, Knepper MA *et al*. Proteomic analysis of lithium-induced nephrogenic diabetes insipidus: mechanisms for aquaporin 2 down-regulation and cellular proliferation. *Proc Natl Acad Sci USA* 2008; 105: 3634–3639
8. Saadi-Kheddouci S, Berrebi D, Romagnolo B *et al*. Early development of polycystic kidney disease in transgenic mice expressing an activated mutant of the beta-catenin gene. *Oncogene* 2001; 20: 5972–5981
9. Storkel S, Eble JN, Adlakha K *et al*. Classification of renal cell carcinoma: Workgroup No. 1. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). *Cancer* 1997; 80: 987–989
10. Peyromaure M, Thiounn N, Scotte F *et al*. Collecting duct carcinoma of the kidney: a clinicopathological study of 9 cases. *J Urol* 2003; 170: 1138–1140
11. Chao DH, Zisman A, Pantuck AJ *et al*. Changing concepts in the management of renal oncocytoma. *Urology* 2002; 59: 635–642

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