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NEPHROLOGY – CASE REPORT

Octreotide reduces hepatic, renal and breast cystic volume in autosomal-dominant polycystic kidney disease

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Abstract A 43-year-old woman with autosomal-dominant polycystic kidney disease (ADPKD) received octreotide for 12 months, and this was associated with a 6.3% reduction in liver volume, an 8% reduction in total kidney volume and stabilization of renal function. There was also a reduction of cyst size in fibrocystic disease of breast. These data suggest that the cyst fluid accumulation in different organs from patients with ADPKD is a dynamic process which can be reversed by octreotide. This is the first report of a case of simultaneous reduction in hepatic, renal and breast cystic volume with preservation of renal function in a patient with ADPKD receiving octreotide.

Keywords ADPKD · cAMP · Fibrocystic disease of breast · Octreotide · Renal function · Volume change

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Introduction

ADPKD is associated with cysts in many organs including kidneys, liver, pancreas, lungs, spleen, ovaries, testes, seminal vesicles, thyroid and uterus. However, there is only a report of cystic changes of the breast along with this disease [1]. Currently, there is no effective treatment available to retard cyst growth and to prevent progression to end-stage renal failure in patients with ADPKD. In addition, apart from invasive interventions such as aspiration-sclerotherapy, laparoscopic or laparotomic fenestration and partial liver resection, no medical treatment to reduce liver volume is available. On the other hand, the treatment of fibrocystic disease of breast sometimes consists also in invasive aspiration of the cyst fluid [2]. There is, however, a high risk of recurrence after cyst aspiration.

Evidence has recently been obtained from animal experiments that activation of the cAMP signalling plays a crucial role in cyst growth and increase in liver and renal volume and that the inhibition of cAMP with somatostatin analogues markedly slows cyst development (hepatic and renal) and deterioration of renal function [3]. In patients with ADPKD, octreotide inhibited renal cyst growth, but hepatic cyst volume was not evaluated in this trial [4]. On the other hand, in a recent study, lanreotide resulted in a significant reduction of liver volume in ADPKD [5]. Therefore, the effect of octreotide in hepatic and kidney volume and in renal function of patients with

ADPKD has not been established. In addition, an effect of somatostatin analogues on cyst growth in fibrocystic disease of breast has not been reported to date.

Case

A 43-year-old woman with ADPKD was referred in June 2006 for routine follow-up. Arterial hypertension was known for 8 years and was treated with telmisartan 80 mg daily and atenolol 50 mg daily. Five years earlier, she was evaluated for bilateral breast masses, and multiple bilateral breast cysts were confirmed by mammography, ultrasonography (US) and magnetic resonance imaging (MRI). A needle aspiration of a breast cyst was performed and cytology showed benign ductal cells. In yearly revision, the larger cyst from her right breast was aspirated and 10–20 ml of fluid was drained on each occasion. She had no complains to date except for transient pain in her breasts, responding to acetaminophen.

In April 2008, the patient presented with abdominal pain and distension. On physical examination, she had hepatomegaly. An abdominal MRI showed a liver volume of 2,704 ml and a total kidney volume of 987 ml. Serum creatinine was 1.37 mg/dl and eGFR (by MDRD formula) was 44.3 ml/min/1.73 m^2. When the patient had been evaluated by ultrasound 3 months earlier, the larger cyst from her right breast measured 27.0 × 8.7 mm in diameter. Because animal and human trials in ADPKD have shown a beneficial effect of octreotide on hepatic and renal cysts [3, 4], our patient was administered octreotide (Sandostatin LAR®) (40 mg/month) i.m. for 12 months. Informed consent for off label therapy (compassionate use) with octreotide during this period was obtained. Except for initial nausea and abdominal cramps after the first injection, the treatment was well tolerated. There was an increase in blood glucose above 115 mg/dl that did not require pharmacologic treatment. Renal function, liver volume and total kidney volume measured by MRI were monitored throughout the treatment phase. In this patient, the volumes of the liver and both kidneys were assessed by MRI at month 0 and 12 and were determined using a manual segmentation protocol. On each MRI section, the outlines of the liver and the kidneys were manually drawn, and the liver and the renal volumes were calculated by multiplying all outline areas by the section thickness and summing the volume of each section.

MRI, 12 months after the start of octreotide, demonstrated a decrease in liver volume of 169 ml, from 2,704 to 2,535 ml (6.3%) (Fig. 1). In addition, there was a reduction in total kidney volume from 987 to 908 ml (8%); left, from 472 to 450 ml (5%); right, from 515 to 458 ml (11%) (Fig. 2). At this time, serum creatinine was 1.41 mg/dl and eGFR was 42.7 ml/min/1.73 m^2. The patient noticed that her fibrocystic breast disease had improved, and 12 months after the start of octreotide, there was no further need for breast cyst aspiration. By ultrasound examination, the largest cyst from her right breast showed a reduction in the longest diameter from 27.0 to 20.1 mm (26%) after 9 months (Fig. 3). By MRI,

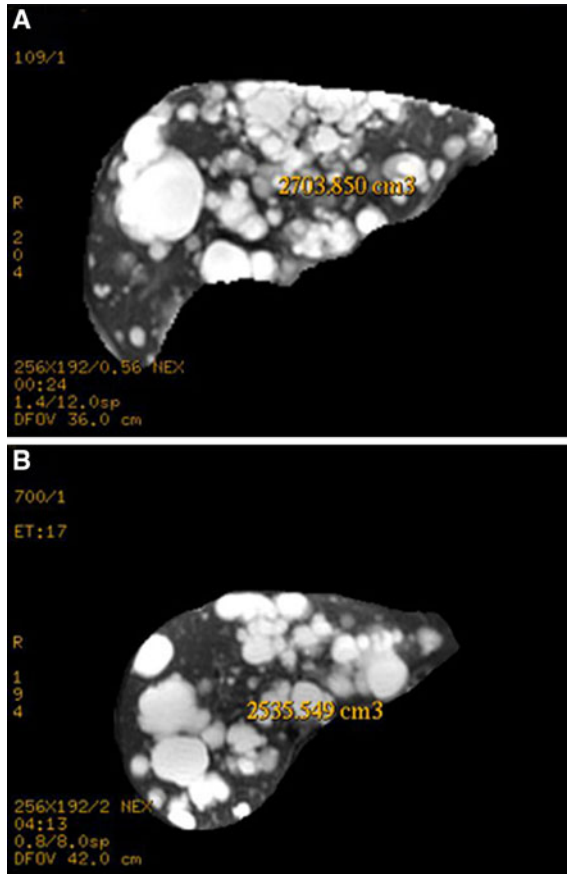

Fig. 1 Octreotide decreased liver volume in ADPKD. MRI prior to (**a**) and after 12 months of treatment (**b**). Volumetry showed a decrease of liver volume from 2,704 to 2,535 ml

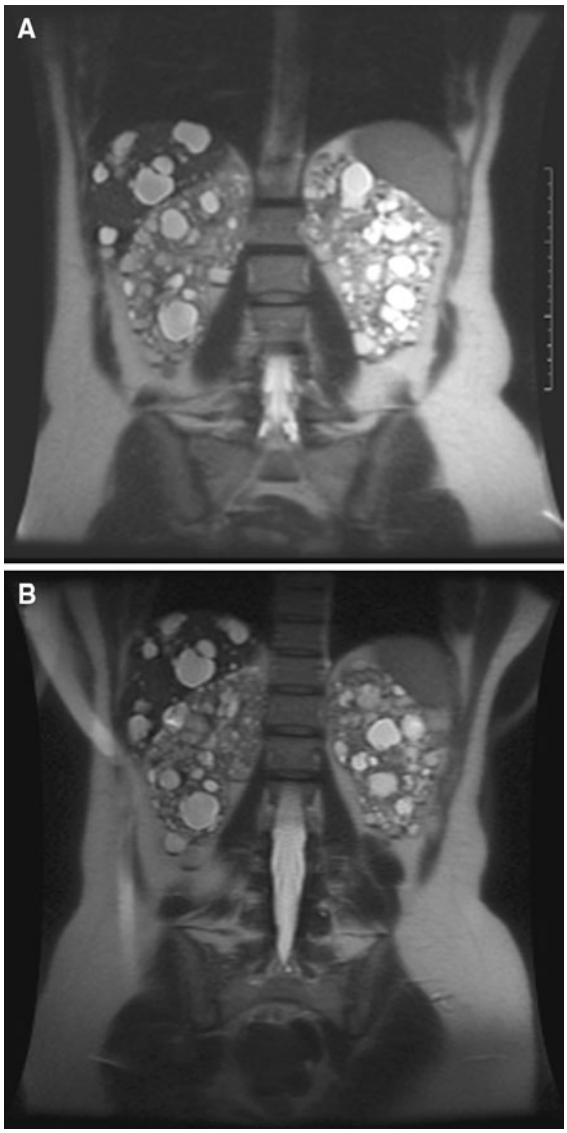

Fig. 2 Octreotide decreased kidney volume in ADPKD. MRI prior to (**a**) and after 12 months of treatment (**b**). Volumetry showed a decrease of total kidney volume from 987 to 908 ml

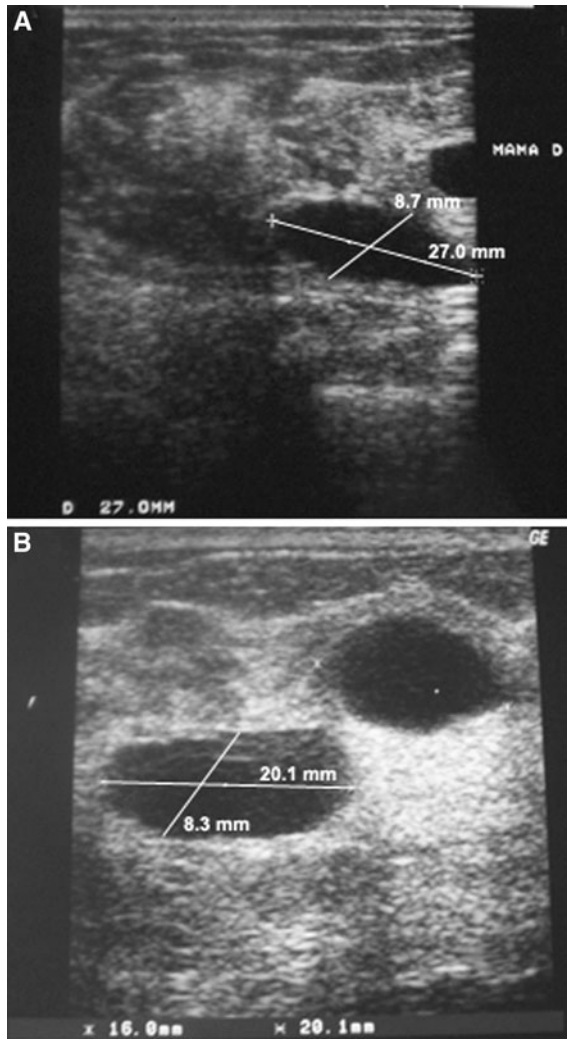

Fig. 3 Octreotide decreased cyst size in fibrocystic disease of breast in ADPKD. Ultrasound of the right breast prior to (**a**) and after 9 months of treatment (**b**). In the right breast, the largest cyst showed a reduction in the longest diameters of 27.0 × 8.7 mm to 20.1 × 8.3 mm

the largest cyst from her left breast demonstrated a reduction in the longest diameter from 34.8 to 17.7 mm (51%) after 12 months (Fig. 4). The treatment with octreotide was continued.

Discussion

Our results demonstrate that injections of octreotide 40 mg given once a month for 12 months resulted in a reduction of liver volume of 169 ml (6.3%) in this patient with ADPKD. In addition, we observed a reduction of total kidney volume of 79 ml (8%). Renal function stabilized during this period (eGFR was 44.3 ml/min/l.73 m^2 before, and 42.7 ml/l.73 m^2 after treatment). Although it was not the primary purpose of our study to demonstrate that octreotide had extrarenal or extrahepatic beneficial effects, we saw that after 9 months the diameter of the largest cyst of right breast decreased by 26% and that after 12 months the diameter of the largest cyst of left breast decreased by 51% with octreotide.

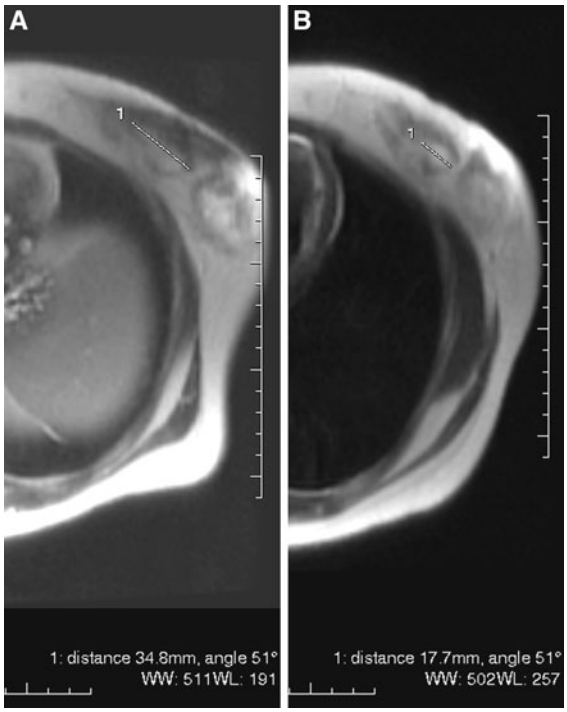

Fig. 4 Octreotide decreased cyst size in fibrocystic disease of breast in ADPKD. Axial MRI of the left breast prior to (**a**) and after 12 months of treatment (**b**). In the left breast, the largest cyst showed a reduction in the longest diameter from 34.8 mm to 17.7 mm, measured with a similar angle

Data from a large observational trial, the CRISP study, indicate that total kidney volume in patients with ADPKD at high risk for renal insufficiency increases by 6.76 ± 3.78% per year and GFR decreases by 5.04 ± 5.86 ml/min/year [6]. Data from the Swiss cohort with milder ADPKD (average size of polycystic kidneys at baseline ~ 1,000 ml) show similar findings with respect to total kidney volume [7]. Treatment with octreotide reduced kidney and liver volume and improved renal function in a polycystic disease rodent model [3]. In patients with ADPKD, a 6-month treatment with octreotide inhibited renal cyst growth, but hepatic cyst volume was not evaluated in this trial [4]. However, the renal function did not change. In addition, a 3- to 6-month treatment with somatostatin analogues in 2 patients with polycystic liver led to impressive reductions in liver volume of 14.9% and 38.3%, respectively. There was also a reduction in kidney volume of 10.1% in one patient with ADPKD [8]. In a recent study, lanreotide (another long-acting somatostatin analogue) 120 mg given once a month for 6 months in ADPKD resulted in a significant mean reduction of liver volume of 5% and of total kidney volume of 1.5%, but increased by 9.9 and 3.4%, respectively, in the placebo group [5]. In addition, lanreotide treatment decreased serum creatinine levels, although this did not reach statistical significance. The differences between octreotide and lanreotide studies might be due to differences in the pharmacologic profile of the two drugs, but also because patients in the octreotide trial had worse renal function and higher total kidney volume at baseline. However, the lanreotide study results were similar with those in our patient, in which octreotide resulted in a decrease of liver and total kidney volume and stabilization of renal function. We treated our patient with octreotide 40 mg, which is equivalent to lanreotide 80 mg, suggesting that lower serum levels were probably present in this patient. In contrast, somatostatin receptor affinity for octreotide is higher compared with that for lanreotide, which may offset the lower serum levels [9]. On the other hand, we administered a 12-month treatment, and it is unclear whether a longer treatment would have demonstrated better results, seeing that experiments in the polycystic disease rodent model suggest that the beneficial effects of somatostatin analogues are time- and dose-dependent [3], i.e. longer treatment results in more substantial effects. Furthermore, little is known about the optimal dosage of somatostatin analogues. We chose the standard dose of octreotide of 40 mg. In addition, we do not know whether the observed effect in this patient is reversed after discontinuation of the drug or if, in case of continuation, octreotide becomes less effective.

How does this effect compare with other therapeutic modalities for ADPKD? We evaluated sirolimus and found that this drug given for 8 months was associated with a total renal volume reduction of 23.5% and with a stabilization of renal function [10]. In another study, treatment with sirolimus for an average of 19.4 months was associated with an 11.9% reduction in polycystic liver volume [11].

To our knowledge, a reduction of cyst volume in fibrocystic disease of breast with somatostatin analogues has not been reported to date. Cyst formation can occur in other diseases besides ADPKD, such as fibrocystic disease of breast [12]. In this condition, fibrosis leads to compression of the breast ducts that

in turn results in cystic dilatation of the proximal segments of the ducts. Breast cysts are presumed lobular lesions in which individual acini or terminal ducts dilate, twist and fold to produce a loculation that enlarges as a cyst. Cyst growth is modulated by cAMP, which stimulates epithelial proliferation and cyst fluid secretion, a process which is inhibited by somatostatin. Autocrine and paracrine ATP and adenosine signalling can be detrimental to ADPKD cyst growth. The pathophysiologic effects could be a continuous stimulation of chloride and fluid secretion into the encapsulated cysts and/or a chronic mitogenic effect on the cells that line the cysts. Not only can this be detrimental to the progression of renal cysts but it could also play a role in extrarenal cysts growth in ADPKD, as well as in polycystic diseases of other organs such as the ovary and the breast [12, 13]. Indeed, cyst fluid in ADPKD and gross cystic disease of the breast share similar compositional characteristics [14]. Therefore, the fact that in this patient, there was no further need for breast cyst aspiration during the 12 months of treatment reinforces the concept that octreotide affects cyst growth in different organs.

In conclusion, we believe that the therapeutic effect of octreotide in ADPKD results from direct reduction of cyst volume. Thus, treatment with octreotide for 12 months resulted in a decrease in liver and kidney volume with preservation of renal function. There was also a reduction of cyst size in fibrocystic disease of the breast. This report suggests that cystic fluid accumulation in different organs from patients with ADPKD is a dynamic process which can be reversed by octreotide. These results, although encouraging, require confirmation and further elucidation by subsequent prospective trials.

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Conflict of interest statements None.

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