Acquired Cystic Kidney Disease in Allograft with Long-standing Poor Function

Doença renal cística adquirida em um enxerto cronicamente disfuncional

INTRODUCTION

Acquired Cystic Kidney Disease (ACKD) is regarded as a common late condition of advanced structural non-cystic renal disorders and expresses its most important features when associated with chronic hemodialysis. It was first recognized in native kidneys of patients submitted to long-term substitutive renal therapy. Its occurrence in chronically rejected kidney allografts is rare. Along with Tuberous Sclerosis Complex and von Hippel-Lindau Syndrome, ACKD is widely known as premalignant lesion.

Some investigators have demonstrated that up to 20% of native kidneys diagnosed with ACKD may harbor tumors. However, whether ACKD in allografts shows the same frequency and behavior is not clear. Herein we report a case of ACKD in a long standing nonfunctional allograft (215 months) which is not associated with malignancy and briefly review the literature on this issue.
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Nephropathy, cyclophosphamide was discontinued and patient returned to hemodialysis. Seven years later, he developed macroscopic hematuria and abdominal pain. In November 2010, computed tomography scan performed pointed out multiple cysts throughout the renal graft cortex. As a result, resection of allograft was performed on December 22nd, 2010.

The excised graft weighed 160 g and measured 11.5 x 7.0 x 3.8 cm. It showed a gross pattern of end-stage chronic disease (Figure 1 and Figure 2). In addition, the cortical parenchyma was diffusely replaced by dozens of unilocular cysts. Internal surfaces were smooth. Most of cystic cavities were smaller than 1.0 cm but size was rather variable ranging from 0.1 cm to 3.2 cm in diameter. Some cavities were filled with bloody content. No tumors or solid lesions were found.

Microscopic evaluation revealed multicystic end-stage disease involving a globally atrophic renal parenchyma. Most cysts presented a single-layered cuboidal or flat clear cell lining epithelium. However, some harbored foci of clear cell papillary hyperplasia (Figure 3). Some epithelial cells showed mild nuclear hyperchromasia while other cystic cavities were filled with recent bleeding. Secondary changes as calcium oxalate deposits and old hemorrhage were observed throughout the specimen (Figure 4). These findings were consistent with the diagnosis of ACKD.

Less than one year after graft resection, the patient was submitted to retransplantation with cadaveric donor (woman, 55 years old, dead due to cerebrovascular accident). The secondary allograft kept adequate function until the last appointment (May 2016). The patient is alive and well after four years of retransplantation and more than twenty three years after his first kidney transplant. During this period, multiple non-related conditions as gout,

Figure 1. General gross aspect indicates end-stage chronic kidney disease.

Figure 2. Multicystic end-stage disease involves globally atrophic renal parenchyma.

Figure 3. Papillary hiperplasia. Some atrophic tubules may be observed in the subjacent parenchyma. (HE, 200X).
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Patients presenting only partially impaired renal function, although cyst formation occurs at a lower rate and severity in this setting. The duration of dialysis in patients with end-stage renal disease often correlates with the incidence of ACKD and renal cell carcinoma in native kidneys. However, few studies have addressed these conditions in transplanted kidneys. Chung et al. related five cases of ACKD in renal allografts. Four were nephrectomy specimens and one was core biopsy specimen.

Duration of allograft in place ranged from 44 up to 80 months. Papillary epithelial hyperplasia was the most common histological finding. Malignancy was found in just one case. Authors suggested that development of tumors could require a longer period than cyst formation. Their thesis is in concordance with the findings of Williams and coworkers who found renal cell carcinoma in an allograft kidney with ACKD after 228 months of placement.

To emphasize that ACKD is not always required for the development of tumors in end stage renal disease setting is important. In a large series of Tickoo et al. composed of 52 patients with end stage renal disease and renal cell carcinoma in native kidneys, 39 patients (75%) presented associated ACKD whereas 13 patients (25%) showed noncystic end stage renal disease.

The pathogenic mechanisms of cyst formation are not completely understood. The uremic status secondary to end-stage renal disease seems to be the main factor of ACKD. Even diseases which cause only partially impaired renal function (eg: creatinine clearance 52-71 mL/min and serum creatinine 1.6 mg/dL) may be sufficient to induce cyst formation. Dialysis may prolong survival, thus allowing ACKD more time to develop. Activation of proto-oncogenes is probably involved.

Papillary hyperplasia in the lining epithelium of cystic cavities is regarded as potential premalignant condition associated with ACKD. Konda et al. investigated the expression of hepatocyte growth factor (HGF) and its receptor (c-met) in kidneys presenting ACKD and renal cell carcinoma. They observed upregulation of HGF and c-met expression in hyperplastic cysts and neoplastic parenchyma.

Similarly, anomalous epithelial proliferation ACKD-associated was aimed by Horiguchi and Ishikawa who investigated immunohistochemical expression of epithelial growth factors on those

**DISCUSSION**

ACKD emerged as a clinically significant condition during the late 1960s and early 1970s with the consolidation and propagation of hemodialysis as main treatment modality to chronic renal failure. In 1977, Dunnill et al. first described ACKD in a series of thirty patients who had been treated by long term intermittent hemodialysis. Fourteen of these patients developed ACKD bilaterally in native kidneys. The authors affirmed that the main complications of the newly recognized condition were hemorrhage and tumor formation. Since then, many different investigators have reached similar conclusions. Other less usual complications include cyst infection, ureteral lythiasis and peripheral blood hyperviscosity.

In spite of being present in the majority of cases, dialysis is not a necessary condition for development of ACKD. Cystic disease may develop in predialytic arrhythmia, hypertension and symptomatic coronary artery disease have emerged and been accordingly treated. The patient has shown good adherence to all therapeutic measures.

**Figure 4.** Oxalate calcium deposits are seen adjacent to hyperplastic epithelium.
lesions. According to them, immunohistoexpression of epidermal growth factor (EGF) and its respective receptor (EGFR) were significantly increased in cysts presenting papillary hyperplasia in comparison to single-lined cysts.

Recently, ACKD has been regarded as a main element for understanding de novo malignance risk in renal retransplanted patients. Kalil et al. compared the risk of cancer in primary transplanted kidney recipients to retransplanted patients in a retrospective study based on large US cancer registries. Among other findings, they showed that patients submitted to retransplant had a higher risk of renal cell carcinoma than the primary transplanted group. Investigators suggested that increased risk might be influenced by ACKD in native kidneys.

In our study, a chronically rejected nonfunctioning renal allograft developed ACKD without tumor formation after 215 months of transplantation. To date, it represents one of the longest intervals for a kidney allograft associated with ACKD ever reported. We believe that the good adherence of our patient to kidney substitutive therapy after functional graft impairment may have favored the absence of malignancy in the transplanted organ.

Also is noteworthy the presence of multicystic pattern in kidney presenting normal weight and dimensions. Oppositely to Autosomal Dominant Polycystic Kidney Disease, ACDK classically shows preservation or decrease in these parameters. Such finding is a constant feature in ACKD and is observed both in native organs and in allografts affected by disease. Therefore, it represents a significant diagnostic criterion which may be accessed by imaging methods. The remaining gross and histological findings in the graft were typical and concordant with clinical and literature data.

Improvement of survival of transplanted patients due to cumulative advances on transplant medicine exposes a growing population to chronic complications of transplant therapy. On this context, ACKD in allograft might become more prevalent. It is not clear yet if ACKD in allografts shows the same frequency and behavior of ACKD in native kidneys. Case reports and systematic reviews might provide new perspectives on this matter. Therefore, more studies should aim at chronic complications of transplant therapy.

References