INTRODUCTION

Chronic renal failure patients on maintenance hemodialysis are frequently associated with the development of multiple and bilateral small renal cysts; these cysts are usually less than 0.5 cm in diameter but can be as large as 2 to 3 cm ***(Arelene et al., 2008)***.

In United States the rate of occurrence of acquired cystic kidney disease (ACKD) are 7-22% in the predialysis population, 44% within 3 years after beginning dialysis, 79% more than 3 years after beginning dialysis, and 90% longer than 10 years after beginning dialysis. The rate of progression appears to slow after 10-15 years of dialysis ***(Dwarakanathan, 2006)***.

The incidence of renal cell carcinoma is 0.18% per year in patients with ACKD compared to 0.005 % in the general population. Renal cell carcinoma occurs approximately 20 years earlier in people with ACKD than in general population. In children, ACKD –associated renal cell carcinoma is rare ***(John, 2007)***.

Male gender, black race and duration of dialysis are primary risk factors. It may occur less frequently in those who are on peritoneal dialysis and may regress after transplantation. Its pathogenesis is not understood but may relate to the activation of proto-oncogenes, which may also

be responsible for the subsequent development of renal cell carcinoma ***(John, 2007)***.

The exact cause of cyst formation has not been identified. One theory suggests that the development of cysts in acquired renal cystic disease (ARCD) is secondary to obstruction of the tubules by fibrosis or oxalate crystals. Another hypothesis suggests the accumulation of growth factors and stimulatory chemicals (uremic toxins) which leads to the development of cysts ***(Wilson, 2004).***

Most patients are asymptomatic, but symptoms may include gross hematuria, flank pain, renal colic, or a palpable renal mass. Hemorrhagic cysts occur in 50% of patients ***(Wilson, 2004)***.

The diagnosis of acquired cystic disease in renal failure is established by ultrasonography, CT scanning or MRI, although each procedure can have false negative results. CT- and MR-based imaging offer increased sensitivity in detecting small cysts over ultrasonograph ***(Arlene et al., 2008)***.

Mild bleeding episodes may be managed with bed rest and analgesics. The identification of mTOR as a possible common pathway to cyst development makes this protein an attractive target for therapy. Rapamycin inhibits mTOR and has been shown to stop kidney growth and even allow regression in kidney size in a mouse model. Patients

treated with rapamycin demonstrated a 25% decrease in kidney volume ***(Andrew and Trout, 2006)***.

Persistent or severe hemorrhage may necessitate nephrectomy or renal embolization. If a 3-cm renal mass suggestive of renal cell carcinoma (RCC) is noted, a partial or radical nephrectomy is indicated ***(Andrew and Trout, 2006)***.

Simple, intermediate, and suspicious cysts rarely require surgical management to relieve pain. Treatment options include aspiration, sclerosis, open resection, endoscopic marsupialization and percutaneous resection, and laparoscopic resection ***(Andrew and Trout, 2006)***.

AIM OF THE WORK

Prevalence and associations of ACKD among heamodialysis patients in Ain Shams University hospital.

Chapter I
RENAL CYSTIC DISEASE

(A) SIMPLE RENAL CYST

Introduction

Renal cysts result from genetic or nongenetic processes, and occur in a variety of diseases in adults and children.

Table (1): Major Groups of Cystic Nephropathies

Disorder	Clinical Features
Hereditary	
Medullary cystic disease	Similar to nephronophthisis but ESRD in adulthood
Nephronophthisis	Small to normal-sized kidneys, hypertension, renal tubular acidosis, ESRD in childhood
Polycystic kidney disease	
Autosomal dominant	Abdominal pain, hematuria, hypertension, large kidneys, extrarenal cysts (liver, pancreas, intestine), ESRD in adulthood
Autosomal recessive	Large kidneys, hepatic fibrosis, hypertension, ESRD in childhood
Congenital	
Renal cystic dysplasia	Associated with urinary structural obstruction or metanephric malformation; degree of dysplasia asymmetric between kidneys
Malformation syndromes	
Ehlers-Danlos	Joint hyperextensibility, increased skin elasticity
Ellis-van Creveld	Short limb dwarfism, polydactyly, heart defects frequently
Goldston	Cerebellar malformations
Ivemark's	Spleen agenesis, cyanotic heart disease, gut malrotation
Jeune's	Dwarfism involving chest, arm, legs
Laurence-Moon	Hypogonadism, mental retardation, retinopathy, polydactyly
Meckel-Gruber	Occipital encephalocele, polydactyly, craniofacial dysplasia
Melnick-Fraser	Branchial fistulae and cysts, preauricular pits or tags, hearing loss
Oral-digital-facial	Partial clefts in lip, tongue, and alveolar ridges; hypoplasia of nasal cartilage; microcysts in kidneys
Trisomy 13	Profound developmental delay, microphthalmia, cleft lip and palate, polydactyly
Trisomy 18	Profound developmental delay, malformations of head, face, hands, and feet
Trisomy 21	Mild to moderate developmental delay, low-set ears, small jaw, congenital heart defects
Tuberous sclerosis	Benign tumors of brain, kidney, and skin
Von Hippel-Lindau	Angioma proliferation in the retina, brain, spinal cord, adrenal glands
Zellweger (cerebrohepatorenal)	Brain and liver defects, developmental delay, high serum iron and copper levels, muscular hypotonia
Acquired	
Isolated simple cysts	Low risk for renal disease or hypertension
Acquired cystic disease	Associated with long-term dialysis; high risk for renal carcinoma

ESRD = end-stage renal disease

(Merck Manual Professional, 2005)

Simple renal cysts are commonly observed in normal kidneys, with an increasing incidence as individuals age ***(Lippert, 2002).*** They are benign asymptomatic lesions that rarely require treatment.

The principal clinical concern is accurately distinguishing simple renal cysts from complex renal cysts that may harbor neoplastic masses. Based upon the initial radiographic evaluation, further study may or may not be required, and some complex lesions that cannot be characterized noninvasively require surgical excision for diagnosis.

Bosniak classification of renal cysts

The incidental finding of lesions in the renal parenchyma is common with the increased use of imaging procedures. Such lesions are usually simple benign renal cysts, complex renal cysts, or neoplasms, although the disorders previously described should also be considered, when appropriate.

To help diagnose and manage these lesions, the Bosniak renal cyst classification system was created ***(Israel and Bosniak, 2005).*** Based upon morphologic and enhancement characteristics with CT scanning, cystic renal masses are placed into one of five different categories. The presence of true contrast enhancement of the lesion (a minimum increased attenuation of 10 to 15 Hounsfield

units) is the most important characteristic separating categories III and IV, which are associated with malignancy in 40 to 90 percent, from the categories I, II, and IIF, which are typically benign processes ***(Israel and Bosniak, 2005):***

Category I: This is a benign simple cyst with a thin wall without septa, calcifications, or solid components. It has the density of water and does not enhance.

Category II: These are benign cystic lesions in which there may be a few thin septa; the wall or septa may contain fine calcification or a short segment of slightly thickened calcification. This category also includes uniformly high attenuating lesions that are less than 3 cm in diameter, well marginated, and non-enhancing.

Category IIF: These cysts, which are generally well marginated, are more complicated than category II, but less so than category III. They may have multiple thin septa or minimal smooth thickening of the septa or wall, which may contain calcification that may also be thick and nodular. There is no measurable contrast enhancement. However, these lesions may have perceived enhancement of the septa or wall, which is due to only subjective (and

not measurable) enhancement when the unenhanced and contrast-enhanced images are compared. This category also includes totally intrarenal nonenhancing high attenuating lesions that are more than 3 cm in diameter. These cysts require follow-up to ascertain that they are non-malignant.

Category III: These are indeterminate cystic masses that have thickened irregular or smooth walls or septa. Measurable enhancement is present. Approximately 40 to 60 percent are malignant (cystic renal cell carcinoma and multiloculated cystic renal cell carcinoma) ***(Harisinghani et al., 2003).*** The remainder, such as hemorrhagic cysts, chronic infected cysts, and multiloculated cystic nephroma, are benign.

Category IV: These lesions (85 to 100 percent of which are malignant) have all the characteristics of category III cysts plus they contain enhancing soft-tissue components that are adjacent to and independent of the wall or septum.

Management by Bosniak category

The following is a general approach to the evaluation of renal cystic lesions based upon initial classification according to the Bosniak CT system:

Category I and II: Further evaluation of Bosniak category I and II lesions is generally not required. In certain instances, repeat ultrasonography at 6 to 12 months to assure stability and a correct diagnosis may be considered. If the clinician is unable to distinguish between a category II and IIF cyst, follow-up imaging is necessary.

Category IIF and III: The optimal approach to renal cystic lesions with indeterminate findings on ultrasonography and CT scanning is uncertain. These lesions are usually Bosniak category IIF or III. As previously mentioned, however, some category II lesions will be included in this category because the features often rely on the quality of the CT scan and the expertise of the radiologist; marked interobserver variation has also been noted when attempting to identify class II lesions that can be safely monitored ***(Richter et al., 2000).***

Category IIF cysts deserve follow-up imaging (hence the "F") to document stability ***(Israel and Bosniak, 2005).*** With this approach, follow-up CT studies are an effective means for managing such complex cysts, in which the absence of change supports benign disease, while progression suggests a neoplastic process. The effectiveness of this approach was best shown in a report of 42 such patients who

had follow-up examinations for two years or more ***(Israel and Bosniak, 2003)*.** Two lesions became more complex with thicker septa; both were found to be cystic neoplasms at surgery. This strategy therefore prevented unnecessary surgery in 95 percent (40 of 42 patients).

Some authorities recommend that all Bosniak category III lesions undergo surgical evaluation, given the high incidence of malignancy (40 to 50 percent) with these findings ***(Israel and Bosniak, 2005)*.** In addition, if the radiologist is unable to clearly distinguish a category IIF from a III lesion, they advocate placing the lesion into the higher category that requires surgery (category III), particularly if a partial nephrectomy is anatomically possible ***(Israel and Bosniak, 2005)*.**

However, with this approach to category III lesions, there would be a significant number of unnecessary surgeries since a significant percentage of patients with indeterminate lesions have benign lesions. To avoid this, two additional modalities, MRI and image-guided biopsy, have been used ***(Israel et al., 2004)*.**

Magnetic resonance imaging

MRI is typically used to evaluate patients with indeterminate lesions ***(Israel et al., 2004)*.** In addition to signal characteristics, MRI evaluates the same morphologic findings as described above for CT scanning: wall

thickening, nodularity, septa, and enhancement. One difference is that MRI does not detect calcification. MRI is especially useful for characterizing internal contents of cysts, such as hemorrhage or mucin, and is more sensitive than both ultrasonography and CT in showing enhancement of internal septations.

The potential value of this approach was illustrated in a series of 37 patients with 55 complex cystic renal lesions who underwent T1-weighted, T2-weighted, and gadolinium-enhanced MRI ***(Balci et al., 1999)*****.** The following frequencies of malignancy were noted with specific radiographic abnormalities:

- 22 percent of 37 lesions that contained fluid of heterogeneous signal intensity
- 44 percent of 32 lesions with intense mural (ie, cyst wall) enhancement
- 63 percent of 16 lesions with mural irregularity
- 71 percent of 14 lesions with a thick wall (>2 mm)
- 75 percent of four lesions with mural masses or nodules, and 50 percent of four lesions with septa

The combination of mural irregularity and intense mural enhancement had the highest correlation with malignancy.

Serial MRI examinations at 3, 6, and 12 months are warranted in patients with indeterminate lesions on gadolinium-enhanced MRI.

Percutaneous needle biopsies:

Preoperative needle biopsies have generally not been recommended for resectable renal lesions because of concern about seeding of the peritoneum. However, biopsy is required prior to percutaneous cryoablation of renal masses. The evaluation of solid renal masses is discussed separately.

The role of biopsy in evaluating an indeterminate renal mass or cyst is likely to grow, as such masses are increasingly being identified with the widespread use of CT and MRI ***(Silverman et al., 2006).*** In patients with indeterminate imaging studies, percutaneous image-guided biopsy appears to be safe and can provide a diagnosis in up to 80 percent cases ***(Silverman et al., 2006).*** This was illustrated in the following reports: One report evaluated 28 patients with a complex cystic renal mass on CT scan who underwent image-guided biopsy: 17 (61 percent) had a malignant lesions (16 renal cell carcinoma, one lymphoma); and 11 had benign disease (six hemorrhagic cysts, three inflammatory cysts, one metanephric adenoma, and one cystic oncocytoma) ***(Harisinghani et al., 2003).*** The biopsy diagnosis was confirmed in all 17 patients who underwent surgical

resection. There was no interval radiologic change at a minimum of one year in the ten patients with benign lesions who did not undergo surgery. A second study evaluated 517 patients in whom image-guided biopsy was performed for renal mass lesions that were classified as indeterminate by imaging (7.2 percent of renal masses). A diagnosis was established in 79 percent, with a malignant lesion found in 44 percent ***(Richter et al., 2000).*** A false diagnosis was made in 1.2 percent, while a diagnosis could not be established by biopsy in 17 percent.

Summary:

With category IIF lesions, we recommend making every attempt to obtain prior studies for purposes of comparison. If such studies are unavailable, many radiologists would recommend an additional imaging study (typically a good quality contrast-enhanced MRI) for further characterization.

With category III lesions, we also try to obtain prior studies for purposes of comparison. In the absence of prior studies or if symptomatic or associated with hematuria, we recommend further imaging evaluation with a good quality contrast-enhanced MRI. If the lesion is still indeterminate, we obtain a surgical consult. Such lesions are either removed or closely followed.

Category IV

Category IV lesions require surgery, with approximately 85 to 100 percent being malignant ***(Curry et al., 2000)*.**

Simple Renal Cysts

Simple renal cysts are observed frequently in normal kidneys. They are the most common renal masses, accounting for roughly 65 to 70 percent of cases ***(Clayman et al., 1984).*** They may be solitary, or multiple and bilateral ***(Slywotzky and Bosniak, 2001).***

Epidemiology:

The prevalence of simple renal cysts varies with the population studied and the imaging modality utilized. These cysts most often occur in patients over the age of 50 as determined from postmortem examination, renal ultrasonography, and/or abdominal CT scanning ***(Terada et al., 2002).*** As examples: One report evaluated 729 patients who underwent ultrasonography for reasons unrelated to the urinary tract ***(Ravine et al., 1993).*** The incidence (in percent) of at least one renal cyst according to age and gender was:

- 15 to 29 years of age — 0 (males); 0 (females)
- 30 to 49 — 1.9; 1.4

- 50 to 69 — 15; 6.7
- >70 — 32.3; 14.6

In this report, bilateral cysts were much less common and were rare in subjects under age 50. A Japanese study of 14,314 individuals undergoing multiphasic health screening programs found at least one renal cyst on ultrasonography in 1,700 (12 percent) ***(Terada et al., 2002).*** A seven-fold increase in prevalence was noted from the fourth to the eighth decade of life (5 to 36 percent). The majority of cysts increased in size over time (2.18 mm per year). A study of 617 adult patients undergoing contrast-enhanced abdominal CT scans unrelated to suspected pathology in the kidney found 213 simple renal cysts (41 percent), with significant increases in number and size of cysts with increasing age ***(Carrim and Murchison, 2003).***

Histopathology

Simple renal cysts are oval or round in shape of varying size, ranging from less than one cm to greater than 10 cm ***(Glassberg, 2002).*** The lining of the cyst is a single epithelial cell layer without renal elements. There is a clear to straw colored fluid that resembles a plasma ultrafiltrate ***(Glassberg, 2002).***