Accepting prospective kidney donors with asymptomatic urinary abnormalities: Are we shooting in the dark?

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CASE PRESENTATION

A 53-year-old Caucasian lady was evaluated in our center as a potential kidney donor. She volunteered to donate a kidney to her brother with whom she shared a 6/6-antigen match. The exact etiology of her brother's end-stage renal disease (ESRD) could not be determined. On evaluation she was noted to be in good health and a review of systems was unremarkable. Family history was significant for functional pituitary tumor leading to acromegaly and diabetes in her father and renal cell carcinoma in her uncle. Physical examination revealed that she was overweight with a body mass index of 31.2 kg/m^2. Her blood pressure was 120/68 mm Hg, her heart rate was 79 beats per minute and she was afebrile. The remainder of the systemic examination was unremarkable.

A transplant donor workup was completed (Table 1). The pertinent abnormality was persistent microscopic hematuria with two out of three urine analyses positive for trace to 1+ blood in dipstick and 1–4 red cells on microscopy. These urinalyses were performed on three separate occasions at least 1 month apart. Urine cultures were negative throughout. Gynecological examination, which included a papanicolaou (PAP) smear, was unremarkable.

The differential diagnosis for the microhematuria was discussed with the patient. The patient was determined to be considered as a candidate for kidney donation and requested that we proceed to a percutaneous renal biopsy in order to definitively identify the cause of hematuria. The renal biopsy findings are shown in Figure 1a–c.

The core comprised of eight glomeruli. Light microscopy showed glomeruli with normal cellularity, well-preserved tubules and interstitium with no fibrosis or active inflammation. The glomerular basement membranes (GBMs) revealed no apparent abnormalities (Figure 1a). Electron microscopy revealed thin GBMs with mean thickness of 242 nm that was consistent with thin basement membrane disease using the criteria by Tiebosch *et al.*[1] (Figure 1b). The mesangium was mildly expanded by small irregular electron-dense deposits in the matrix. Immunofluorescence was significant for diffuse, fine-granular deposition of immunoglobulin (Ig)A (lambda stronger than kappa) in the mesangial areas (Figure 1c). A pathologic diagnosis of thin basement membrane disease and Haas class I IgA nephropathy (IgAN) was made.

CLINICAL DIAGNOSIS

Thin basement membrane abnormality and IgAN in an otherwise healthy patient evaluated for kidney donation.

FOLLOW-UP

The patient was counseled that kidney donation would not be possible. Follow-up in the Chronic Kidney Disease clinic was recommended. She was started on an angiotensin-converting enzyme inhibitor (Lisinopril 5 mg/day) and fish oil (12 g each day). At her most recent visit to the clinic, she was asymptomatic. She indicated that she was taking her Lisinopril regularly but her adherence to fish-oil therapy was at best sporadic. Her renal function was stable (serum creatinine of 0.9 mg/dl and negligible albuminuria).

DISCUSSION

The growing disparity between the supply and demand for transplantable organs has added a tremendous strain on an already overburdened, rapidly expanding transplant waiting list. Consequently, significant number of ESRD patients die owing to longer waiting time. While the supply of deceased

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Kidney International (2007) **71,** 173–177. doi:10.1038/sj.ki.5001940; published online 1 November 2006

Received 21 April 2006; revised 20 August 2006; accepted 29 August 2006; published online 1 November 2006

Table 1 | Transplant donor workup

Urine dipstick	pH 5.0, SG 1.014, trace blood, no protein
Urine microscopy	3–5 RBCs, 1–3 WBCs, no casts, no dysmorphic RBCs, and trace bacteria
Complete blood count	Hb 15 g/dl, WBC 9.11 K/μl, platelets 359 K/μl
Renal function test	BUN 16 mg/dl, creatinine 0.8 mg/dl
Glucose	76 mg/dl
HIV and Hepatitis screen	Negative
24 h Urine collection	GFR 121 cc/min, no microalbuminuria
Cystourethroscopy and bladder washings	Negative for lower urinary tract source of bleeding
CT and MRI scans of the urinary tract	Small benign cyst in the upper pole of left kidney, otherwise normal

BUN, blood urea nitrogen; CT, computed tomography; GFR, glomerular filtration rate; Hb, hemoglobin; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; RBCs, red blood cells; SG, specific gravity; WBCs, white blood cells.

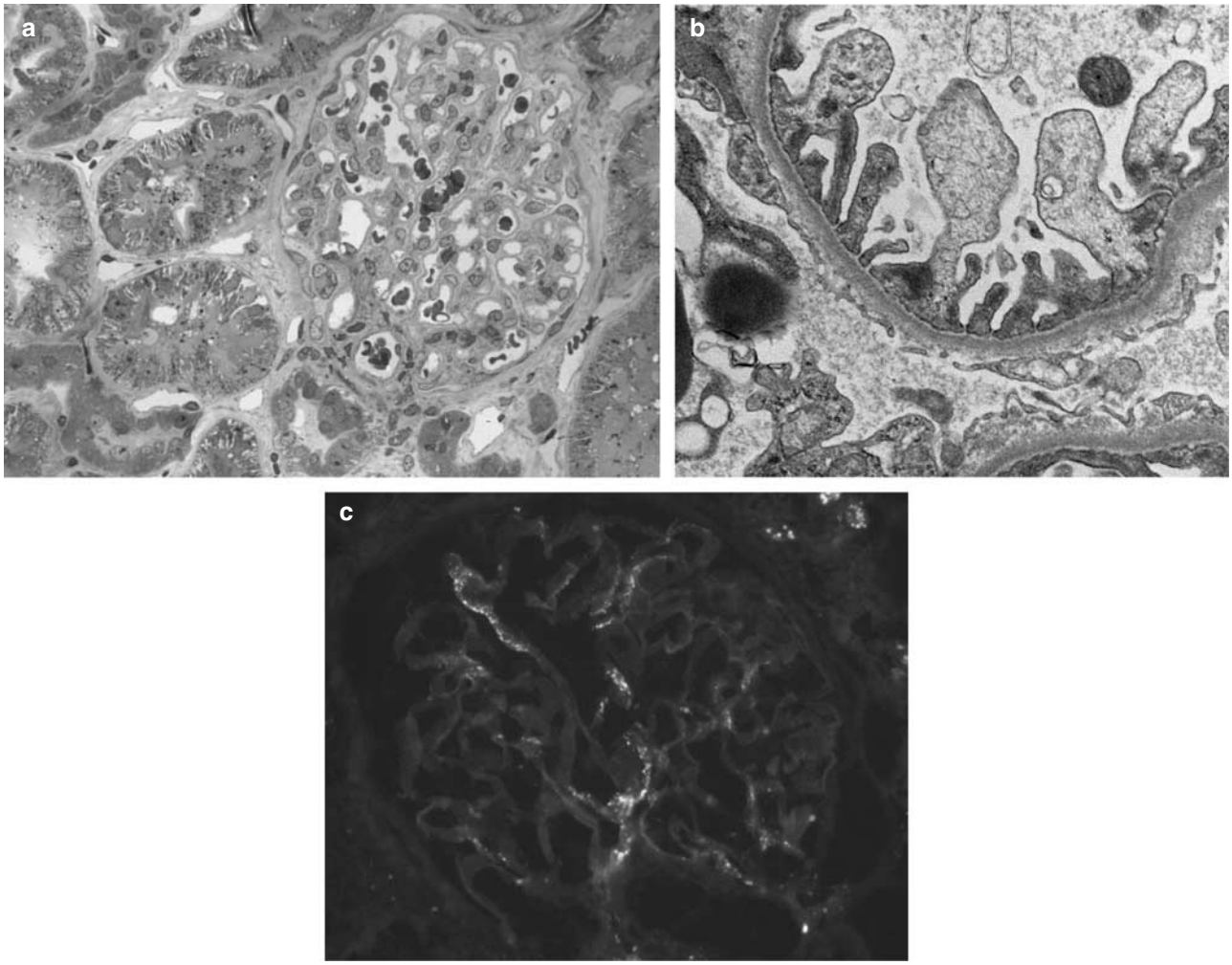

Figure 1 | Renal histopathology. (**a**) Light microscopy of the kidney cortex: The glomerulus, one arteriole, and the surrounding tubules show a normal appearance. There are no inflammatory lesion seen, and the mesangium appears delicate, without significant expansion of the matrix or hypercellularity (toluidine blue semi-thin epoxy section). (**b**) Electron micrograph of the glomerular capillary wall: the endothelium and the foot processes of the visceral epithelial cells are well preserved. The lamina densa of the GBM is attenuated and thin. (**c**) Immunofluorescence microscopy image reveals discrete, fine-granular staining for IgA in the mesangial areas; the reactivity for lambda light chains was slightly stronger than that for kappa light chains. All other Igs and complement components were negative.

donor kidneys has almost plateaued in most western countries, live kidney donation is the only currently available alternative to improve transplantation rate. Living kidney donation has already surpassed deceased donor kidney transplantations in some countries and is rapidly expanding in the remaining countries globally. The prospective donor pool is growing as the life expectancy of the population is increasing. There is a growing pool of relatively healthy but aged individuals to draw from for kidneys. These individuals represent a population of 'marginal donors' – individuals at

higher risk of cardiovascular disease, the presence of prehypertension or treated mild hypertension, obesity, the metabolic syndromes, and the presence of asymptomatic urinary abnormalities such as hematuria or microscopic hematuria. Whether these urinary abnormalities herald the later development of kidney disease remains unclear. However, in the past because of a higher perceived long-term risk, a significant proportion of these candidates would have been denied the option of donating a kidney. On the other hand, some experts have argued that if the risk to the potential donor is only minimally increased, these potential and yet relatively marginal donors be considered as viable candidates and should be accorded the right to determine for themselves whether to take the risk of donating a kidney. In these situations, input from an ethics committee may be helpful. In this paper, we discuss the diagnostic workup, differential diagnosis, and implications of accepting these patients for kidney donation in the context of a case that presents with asymptomatic urinary abnormalities.

Isolated, persistent microscopic hematuria

Microscopic hematuria noted in previously asymptomatic, otherwise healthy potential kidney donors is an increasingly common finding in the workup of kidney donors. Persistent hematuria is defined as three or more red blood cells per high-power field on microscopic evaluation of urinary sediment from two of three properly collected urinalysis specimens.[2] Koushik *et al.*[3] observed that in the University of Minnesota kidney donor-screening program, the incidence was 2.7% among 512 consecutive donor evaluations.

WORKUP FOR MICROSCOPIC HEMATURIA

A minimum of two urine dipstick tests should be performed on separate occasions during the course of the donor assessment to exclude the possibility of intermittent microscopic hematuria. The dipstick is the most reliable and sensitive test (can detect even 1–2 red blood cells per high-power field). Hence, a negative dipstick can reliably exclude clinically significant hematuria.[4] An examination of fresh-centrifuged urine sediment for the presence of red cells and cellular casts could point to the possibility of glomerular bleeding. Routine mid stream urine specimens without centrifugation will not reliably exclude hematuria. A persistent hematuric state as detected by two or more urinalyses over at least 1-month period, in the absence of obvious factors such as menstruation or infection requires full investigation. An algorithm for the workup of hematuria in a kidney donor is shown in Table 2.

Isolated hematuria could result from glomerular bleeding or secondary to extraglomerular causes like nephrolithiasis, urothelial malignancy, and prostatic disease (Table 3). Glomerular bleeding, in most cases, is due to one or more of three disorders: thin basement membrane nephropathy (TBMN, also called benign familial hematuria), IgAN, and Alport's syndrome (AS, also known as hereditary nephritis) or a carrier state. A careful history and renal functional assessment of the prospective donor, as well as repeated urinalysis on all family members can suggest the type of inheritance and the most likely genetic basis of the disease. The clinical evaluation should include any previous history of kidney stones, symptoms of pain, dysuria or prostatism, and a family history of hematuria. Hypercalciuria and hyperuricosuria are shown to be important causes of isolated hematuria both in children and adults. Both disorders are often associated with a positive family history and could be screened by analysis of a 24-h urine collection sample.[5,6] In these patients, microscopic hematuria is mostly secondary to micro- or macrolithiasis. However, with the increasing age of prospective kidney donors, it is essential to rule out urothelial malignancy by performing urine cytology, cystourethroscopy, and renal imaging in those with persistent microscopic hematuria. Renal ultrasound could be used to detect structural pathology such as cysts, neoplasia, and tumors, but its ability to detect small tumors is quite limited. Instead for this reason, computed tomography with intravenous

Table 2 | Algorithm to investigate microscopic hematuria in donors

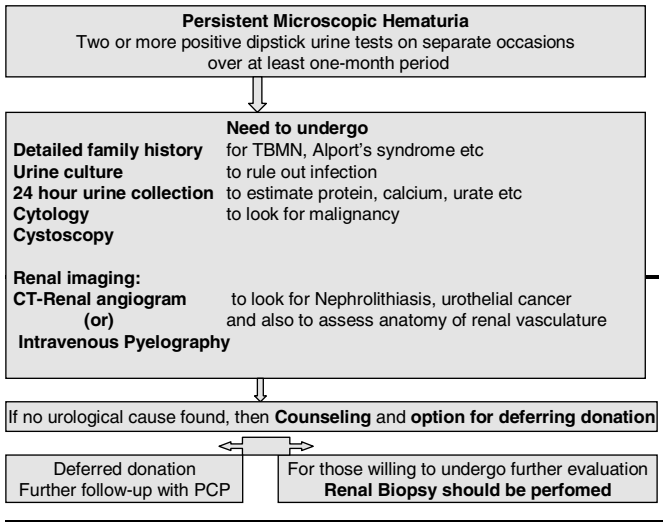

Table 3 | Causes of persistent microscopic hematuria

(A) Glomerular bleeding (common causes, not associated with proteinuria or casts)

1. TBMN
2. AS (early stage) or carrier state
3. IgAN

(B) Extraglomerular bleeding

1. Stone disease
2. Hemoglobinopathy (SS/SA hemoglobin)
2. Polycystic kidney disease
3. Benign prostatic hyperplasia (elderly donors)
4. Malignancy (bladder, kidney, prostate)
5. Arteriovenous malformations and fistulas
6. Schistosomiasis (in endemic areas)
7. Hypercalciuria, hyperuricosuria, etc.

AS, Alport's syndrome; IgAN, IgA nephropathy; TBMN, thin basement membrane nephropathy.

contrast is recommended. Intravenous pyelography used to be the test of choice but is not recommended because it entails extensive exposure to contrast and is quite a lengthy and inconvenient procedure.

Prospective kidney donors should be informed that the presence of persistent, isolated, asymptomatic microscopic hematuria generally precludes the continued possibility of donation. Most donors drop their candidacy at this point and a biopsy is often unnecessary, as the presumptive diagnosis is usually quite clear and the overall long-term prognosis is excellent. If the potential donor candidate remains determined to proceed with a workup then a biopsy is essentially the next step in the workup. As mentioned earlier, kidney biopsy, in most cases, is likely to reveal IgAN, TBMN, or AS. Sobh *et al.*[7] investigated 30 potential living related kidney donors with isolated hematuria in Egypt. AS or a carrier state was found to be the most common cause (25/30), followed by isolated C3 deposits disease (3/30), IgAN (1/30), and IgM nephropathy (1/30). They attributed this much higher prevalence of AS possibly to higher incidence of consanguineous marriages in their population.

Better risk stratification through accurate diagnosis

Patients with AS and IgAN are not candidates for donation. So it is very important to differentiate cases that resemble TBMN but actually represent Alport's carrier state or an early stage of AS. Clinical features of these conditions overlap and TBMN and AS share some histological abnormalities (Table 4). TBMN is a common, mostly benign renal condition and is transmitted in an autosomal-dominant manner. So screening the first-degree relatives is helpful in making this diagnosis in conjunction with histological parameters. History of renal impairment among family members is rare, contrary to what we observe in Alport's carrier families. Most individuals with TBMN have normal renal function. Renal impairment with progression to end-stage renal failure is rare.[8] Proteinuria and hypertension are the only known risk factors. Renal impairment in TBMN may represent an aggressive variant or owing to coexistent renal lesions (e.g. IgAN or focal segmental glomerulosclerosis) or even misdiagnosed Alport's.

In contrast to TBMN, AS is a less common but progressive form of glomerular disease with associated sensory neural hearing loss and ocular abnormalities. AS is a genetically heterogeneous disease with X-linked recessive (85%), autosomal-recessive (15%), and autosomal-dominant (5%) variants. Women with Alport's carrier state carry a small but significant risk (8–12% in one series by Dagher *et al.*[9]) of renal failure. Electron microscopy and immunohistochemistry may help differentiating TBMN from AS. Electron microscopy in AS typically shows GBM lamellation and thickening, but these changes may be absent or patchy in female carriers and in early disease. Analysis of type IV collagen expression by immunostaining will show no staining in most patients with Alport's, discontinuous staining in female carriers, and normal staining in TBMN.[10] However, it is important to note that in AS, staining for subtypes of type IV collagen is not always abnormal. In fact, a normal distribution of staining is seen in a significant minority of cases. Among individuals with ongoing suspicion or inconclusive pattern, for absolute exclusion of asymptomatic carrier state, molecular genetic testing would be extremely helpful.[11] However, genetic testing for AS is commercially available only in very few centers and its interpretation could be limited owing to the large number of potential mutations.

Implications for kidney donation

No patient with apparent TBMN should be considered as a donor if there is a family history of progressive renal disease, any evidence of extrarenal manifestation (i.e. sensorineural hearing loss or conus lenticularis) or of the presence of GBM lamellation. It is also generally accepted that TBMN patients with risk factors for progressive disease such as hypertension, proteinuria, or overt renal insufficiency should not be accepted as donors. However, there still remains some controversy regarding whether patients with TBMN with isolated hematuria should be accepted as donors.[12,13] It is important to note, however, that it is even more controversial to consider patients with heterozygous *COL4A5* genetic defect as live renal transplant donors. Although renal donation with parents to their children (mother to son with X-linked Alport's and father to daughter with autosomal-

Table 4 | Distinguishing factors for the three common causes of glomerular bleeding

		TBMN	Female carriers of X-linked Alport's	IgAN
1.	Prevalence	Common	Uncommon	Common
2.	Family history of hematuria	Common	Common	Only in isolated cases
3.	Family history of renal failure	Uncommon	Common	Usually absent
4.	Family history of deafness	Uncommon	Common	Absent
5.	Deafness at adulthood	Rare	$<$10% incidence	Absent
6.	Retinopathy and lenticonus	Absent	Rare	Absent
7.	GBM by EM	Thinned	Thinned with regions of lamellation	Normal
8.	Type IV collagen in GBM	α3–α5 chains all present	Normal α3–α5 chain distribution or patchy loss	Normal
9.	IgA staining	Negative	Negative	Positive with C3 and IgG in mesangium
10.	Genes affected	*COL4A3/COL4A4*	*COL4A5*	*6q22–23*

EM, electron microscopy; GBM, glomerular basement membrane; Ig, immunoglobulin; IgAN, IgA nephropathy; TBMN, thin basement membrane nephropathy.

recessive Alport's) with AS has been reported with good short-term outcome for donor and recipient, the actual long-term risk remains unknown.[12–14] However, again it has to be emphasized that, at least in our opinion, any of these patients with evidence of extrarenal manifestations, hypertension, or proteinuria should be deferred from donation.

Isolated proteinuria in prospective donors

Isolated proteinuria is not an uncommon finding during donor workup. Currently in most centers, individuals with proteinuria of greater than 150 mg/day will be disqualified as potential kidney donors. A persistent proteinuric state should be differentiated from transient or orthostatic proteinuria. Evaluation of patient with mild proteinuria should include testing the urine on at least two other occasions. The urine sediment should also be examined for other signs of glomerular pathology such as hematuria, red cell casts, etc. Persistent proteinuria can be evaluated with a 24-h urine collection or a random total protein-to-creatinine ratio. Renal imaging studies will help to rule out structural renal pathology. In the Okinawa General Health maintenance Association study,[15] a strong graded relationship between dipstick-positive proteinuria and ESRD in general population was noted. However, the rate of ESRD was only less than 2% in those with mild proteinuria during almost two decades of follow-up. In an effort to increase live donor transplantation rate, Karpinski *et al.*[16] proposed slight relaxation of current rigid criteria. They defined potentially acceptable proteinuria as 150–300 mg/dl. By accepting living donors with mild proteinuria or mild hypertension, they estimated that, a modest 3% increase in transplantation rate could be achieved in their waitlisted ESRD population. In our own practice, patients with mild proteinuria (150–200 mg/24 h of proteinuria) but who are normoalbuminuric (<30 mg albumin/g creatinine for male and <35 mg albumin/g creatinine for female subjects) may be acceptable as kidney donors as long as there are no other risk factors (e.g. the presence of even mild hypertension).

Although many follow-up studies of ideal donors reported no significant increase in hypertension, proteinuria, or renal impairment, some observed slight increase in these outcomes compared to healthy siblings or age-matched controls. Based on this, one should assume that the actual long-term risk for these marginal donors would be higher, but at present actual risk is not quantifiable. Individuals with this presentation are likely to represent older individuals like parents of potential recipients, with much higher motivation to donate for their loved ones. At present there is no uniform agreement and the acceptance of these marginal donors is variable between different transplant centers.

CONCLUSION

Asymptomatic urinary abnormalities in the prospective donor population need a thorough evaluation in order to identify the underlying pathology. In addition, careful assessment of the patient's family history and a meticulous screening of family members for urinary abnormalities is important in screening for underlying kidney disease. Because of limited long-term outcome data, the actual risk of kidney donation in these individuals is currently unknown. In the interim, a full explanation of possible outcomes after kidney donation should be offered to the very motivated donors. Each case has to be carefully assessed in the context of the donor and recipient's wishes and their medical needs. Input may also be needed from an ethics committee. Notwithstanding, a further understanding of the pathologic, molecular, and genetic features of these conditions would be very helpful in stratifying those with least risk of kidney donation. Similarly, in future, the long-term follow-up and outcome studies in these 'marginal donor population' would be invaluable in clarifying the above uncertainties.

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