Published in final edited form as:

Transplantation. 2015 April ; 99(4): e27–e28. doi:10.1097/TP.0000000000000643.

Lupus After Kidney Donation: A Case Report with Implications for the Evaluation of Potential Donors with a Family History of Lupus

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Abstract

We report a case of lupus occurring in a 52 year-old woman approximately 2 years after donating a kidney to her brother who had end-stage-renal-disease on the basis of lupus nephritis (LN). At the time of donation, the patient had been asymptomatic with a normal physical examination, laboratory and imaging studies. At the time of her diagnosis of lupus she was found to be ANA negative but positive for anti-double stranded DNA. Testing for markers of autoimmune disease was not performed prior to donation. There is little guidance in the literature on risk stratification for potential living kidney donors with a family history of systemic lupus erythematosus (SLE) and LN. The utility of routine ANA testing for all potential kidney donors is limited however it may help inform the risk-assessment of possible donors with a family history of SLE. We suggest that ANA screening be done for all potential kidney donors with first-degree relatives who have SLE. More complete screening for autoimmune markers and greater caution should be used when assessing potential kidney donors with SLE-affected first-degree male relatives.

Keywords

Kidney transplantation; living donors; evaluation; systemic lupus erythematosus; lupus nephritis

Introduction

The excellent long-term outcomes (1, 2) observed for living kidney donors, in part, relate to them having undergone a thorough evaluation prior to donation. It is considered mandatory

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Disclosure statement:

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

that the donor screening process includes an individualized assessment of future risks of chronic kidney disease (CKD) and end-stage-renal-disease (ESRD) (3–5).

One poorly defined aspect of the evaluation of potential kidney donors concerns the degree to which there is increased future risk of developing systemic lupus erythematosus (SLE) and lupus nephritis (LN) for those who have a family history.

In recent years, studies assessing the genetics of familial SLE have provided new insights into genetic susceptibility and the interpretation of the results of anti-nuclear antibody (ANA) testing (6). One scenario of particular relevance to the evaluation of related living kidney donors is where the intended recipient is a male with ESRD due to LN. In this situation, the risk of familial LN is increased substantially (7). We report a case of lupus occurring in a female donor following kidney donation to her brother who had developed ESRD secondary to LN.

Case

A 50 year-old woman was evaluated for possible kidney donation. She had previously been in good health and was on no medications. In her responses to screening survey questions and during a subsequent review-of-systems, she reported no complaints. Her family history was significant for a brother with SLE and LN resulting in ESRD. She also had a male first cousin who had been diagnosed with SLE but no other family history of autoimmune or connective tissue disease (CTD). The physical examination was normal. Selected laboratory investigations are detailed in Table 1. Computed tomographic angiography revealed normal and equal-sized kidneys. The patient proceeded to donate her left kidney to her brother *via* laparoscopic nephrectomy without perioperative complications. When seen in clinic one year following donation, she reported feeling well. Serum creatinine (SCr) was 1.1 mg/dL (96 μmol/L) and there was no proteinuria. Urinalysis showed trace blood but was otherwise negative.

Approximately 2 years following donation, the patient developed a malar rash, fatigue and morning stiffness. She reported no fevers or other constitutional symptoms. Her BP was 130/75 mmHg. No additional abnormalities were noted on physical examination. Her ANA was found to be negative but she was found to persistently test positive for anti double-stranded DNA (dsDNA) and low C4 levels with normal C3. There was no evidence of LN on the basis of blood and urine testing. Table 1 details the results of selected laboratory testing at that time.

One year following a clinical diagnosis of lupus by her rheumatologist (in the absence of meeting formal American College of Rheumatology SLE classification criteria, which were formulated as research, not clinical diagnostic, criteria (8)), her renal function remains stable and she has not had further manifestations of autoimmune disease after having started treatment with Plaquenil 400 mg po od.

Discussion

To the best of our knowledge, this is the first reported case of lupus occurring following kidney donation. While the patient has no evidence of renal involvement at this time, she is now at increased risk of developing LN. Furthermore, relative to someone with lupus and both kidneys she is at a greater risk of consequent CKD and ESRD (9). This case serves to highlight recent studies that are relevant to the assessment of possible kidney donors with a family history of SLE.

Current Recommendations For Evaluation of Possible Kidney Donors with a Family History of SLE

There are few recommendations regarding the evaluation of potential donors with a family history of SLE. This topic was not addressed by The Amsterdam Forum on the Care of the Live Kidney Donor (3) or in the recently developed Organ Procurement and Transplantation Network (OPTN) policy on the evaluation of living kidney donors (10). The OPTN policy does state, however, that hospitals must "develop and comply with a protocol for inherited renal disease[s] as indicated by family history" (10). Although LN may not always be considered an inherited renal condition, the risk is certainly increased in family members (6).

To our knowledge, the only previous review to consider this issue is by Pham *et al.* (2007) and was published as part of the *American Journal of Kidney Diseases* 'Core Curriculum' series (11). The authors made several suggestions regarding the evaluation of potential donors who might be at increased risk of subsequently developing SLE (11). For those with a first-degree relative affected by SLE, they recommended screening with ANA and complement levels. They also suggested that testing for antiphospholipid antibodies be done at the discretion of the clinician. Lastly, it was recommended that ANA-positivity in this context should preclude donation on the basis of studies showing up to 12% of first-degree relatives of those with SLE are also affected (11).

Genetic Studies of Familial Systemic Lupus Erythematosus: Added Risks for 1st-Degree Relatives of Affected Males

SLE occurs when genetically predisposed individuals encounter an environmental trigger or triggers (12). While SLE is known to occur in families, inheritance is polygenetic and approximately 40 predisposing genes have been identified (6). Each predisposing gene likely makes a distinct contribution to the overall risk of developing SLE as well as to determining the age-of-onset and clinical features - such as the development of LN - for those who are ultimately affected (12).

While women are more likely to be diagnosed with SLE by a factor of approximately 10:1 (13), men are more likely to have severe disease including LN (14). A study by Stein *et al.* (2002), demonstrated that women with SLE who have at least one affected first-degree relative who is male are also more likely to have severe disease with kidney involvement (7). In addition, these same authors showed that the prevalence of renal disease (with or without a formal diagnosis of SLE using American College of Rheumatology diagnostic criteria) is

significantly increased in female family members of men with SLE as compared to women with an affected female relative (68% versus 43%; P = 0.002). Subsequent studies suggest that for families with only affected male relatives, the etiology of SLE occurrence likely relates to a relatively greater genetic predisposition than is present in families with familial SLE but no (or relatively fewer) affected males (15). Although not studied directly, based on the current evidence and highlighted by our case, it can be inferred that the future risks of developing SLE and LN may be especially elevated for potential kidney donors who are first-degree relatives of SLE-affected men.

Implications of Positive Anti-nuclear Antibody Testing

The presence of autoantibodies, as manifested by ANA-positivity, is found in the majority of those affected by SLE several years prior to the onset of clinical disease (16, 17). Regardless, the clinical utility of screening ANA testing is limited since the test is sensitive but not specific for the future development of SLE: ANA-positivity is found in up to 25% of the general population (18) and even high-titre positivity infrequently heralds clinical disease (19). Nonetheless, given that even modestly increased risks may be considered unacceptable in the context of kidney donation, some experts, as described previously, have suggested that ANA-positivity in a first-degree relative with SLE is a contraindication to donation (11). A recent case-series reported on 12 patients with a positive-ANA test prior to having donated a kidney (20). After 5 years of post-donation follow-up, none of these patients had developed clinical signs or symptoms of SLE (20). It must be noted that none of these patients had a family history of SLE, the median titre level was low (1:100) and the number with high-titre ANA-positivity (≤1:640) was not reported (20). The titre level is a relevant consideration when evaluating the future risk of SLE. In a study of 62 patients with high-titre ANA-positivity and no initial diagnosis of CTD, 5 (8%) went on to develop CTD over a mean follow-up time of 11.5 years (19). The applicability of this finding to the asymptomatic potential-donor population is somewhat limited: the study patients did not meet formal diagnostic criteria for CTD at the time of ANA testing however they were presenting to family doctors or rheumatologists with complaints that prompted the ANA testing to be done (19). In addition, no information regarding family history of SLE or other CTD was reported (19).

Regarding the impact of having a first-degree male relative with SLE on the results of ANA-testing, one study of multicase families is of interest: among families in which all the SLE patients were men, all of the 14 female first-degree relatives were ANA-positive. Among families in which at least one SLE patient was a woman, only 19 of 48 (40%) female first-degree relatives had a positive ANA (p = 0.0006 compared to the relatives in the families with all male SLE) (15). Our patient's persistent ANA negativity and anti-dsDNA positivity is atypical of what has previously been reported in this context.

In addition to ANA, autoantibodies to extractable nuclear antigens such as anti-RNP, anti-Sm, anti-Ro/SSA and anti-La/SSB as well as anti-dsDNA also appear prior to the onset of SLE (16). The presence of any of these antibodies may be more specific for progression to SLE than only a positive ANA, with anti-dsDNA and anti-RNP appearing on average only 2 years prior to SLE onset (16).

Conclusions

To our knowledge, this is the first case report of a patient developing SLE after kidney donation. One interesting aspect of this case is that our patient donated a kidney to her brother who had a history of LN and several studies now suggest relatively increased risks for first-degree relatives of men affected by SLE (7, 12, 15).

Currently, there is insufficient evidence to make definitive recommendations regarding the evaluation of potential kidney donors with a family history of SLE. Nonetheless, we suggest that, while ANA testing should not be done routinely for all potential donors, all those with a family history of SLE or other CTD should get ANA testing. The risks for patients with negative, low- or high-titre ANA results have not been clearly defined however it would seem prudent to exercise greater caution when considering donations from those with low-titre ANA positivity and that, in most cases, high-titre positivity should preclude donation in those with a family history of SLE. Potential donors with high-titre ANA positivity or other SLE-related autoantibodies should be excluded as donors. For those with affected first-degree male relatives, more intensive screening that includes ANA, ENA, C3, C4 and anti-dsDNA should be undertaken. Regardless of the results of ANA testing, given the evidence that first-degree relatives of men with SLE may be at especially increased risks of future SLE and LN, this case highlights that particular caution is indicated when evaluating potential kidney donors with this particular family history.

Acknowledgments

The authors thank the patient who is the subject of this case report for providing additional history and for reviewing and agreeing to submission of the manuscript. The authors also thank Ms. Mary Rada and Ms. Brenda Cyr-Mockler who assisted with data collection. This work was supported in part by an NIH Rheumatic Disease Center of Excellence.

Abbreviations Used

ANA	anti-nuclear antibody
Anti-dsDNA	anti double-stranded deoxyribonucleic acid
BP	blood pressure
CKD	chronic kidney disease
CTD	connective tissue disease
ESRD	end-stage-renal-disease
LN	lupus nephritis
OPTN	Organ Procurement and Transplantation Network
SCr	serum creatinine
SLE	systemic lupus erythematosus

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Table 1

Selected laboratory testing prior to kidney donation and two years after donation

Test	Results	
	Prior to Donation	**Two Years After Donation**
Serum creatinine	0.7 mg/dL (63 μmol/L)	1.1 mg/dL (99 μmol/L)
eGFR	87 mL/min/1.73 m^2	51 mL/min/1.73 m^2
Urinalysis	#1: Trace blood, negative for protein, leukocytes #2: Negative for blood, protein, leukocytes	Negative for blood, protein, leukocytes
Hemoglobin	135 g/L	130 g/L
White blood cells	8.3×10^9/L	7.3×10^9/L
Platelets	312×10^9/L	322×10^9/L
ANA	----	Negative
Anti-dsDNA	----	Positive
C3	----	1.01 g/L (normal)
C4	----	0.13 g/L (low)

eGFR, estimated glomerular filtration rate

ds-DNA, double stranded DNA

ANA, anti-nuclear antibody

Anti-dsDNA, anti-double stranded deoxyribonucleic acid