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ORIGINAL ARTICLE

Retrospective Cohort Study

Preemptive living donor kidney transplantation: Access, fate, and review of the status in Egypt

Rabea Ahmed Gadelkareem, Amr Mostafa Abdelgawad, Ahmed Reda, Nashwa Mostafa Azoz, Mohammed Ali Zarzour, Nasreldin Mohammed, Hisham Mokhtar Hammouda, Mahmoud Khalil

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Abstract

BACKGROUND

Preemptive living donor kidney transplantation (PLDKT) is recommended as the optimal treatment for end-stage renal disease.

AIM

To assess the rate of PLDKT among patients who accessed KT in our center and review the status of PLDKT in Egypt.

METHODS

We performed a retrospective review of the patients who accessed KT in our center from November 2015 to November 2022. In addition, the PLDKT status in Egypt was reviewed relative to the literature.

RESULTS

Of the 304 patients who accessed KT, 32 patients (10.5%) had preemptive access to KT (PAKT). The means of age and estimated glomerular filtration rate were 31.7 ± 13 years and 12.8 ± 3.5 mL/min/1.73 m^2, respectively. Fifty-nine patients had KT, including 3 PLDKTs only (5.1% of total KTs and 9.4% of PAKT). Twenty-nine patients (90.6%) failed to receive PLDKT due to donor unavailability (25%), exclusion (28.6%), regression from donation (3.6%), and patient regression on starting dialysis (39.3%). In multivariate analysis, known primary kidney disease (P = 0.002), patient age (P = 0.031) and sex (P = 0.001) were independent predictors of achievement of KT in our center. However, PAKT was not significantly (P = 0.065) associated with the achievement of KT. Review of the literature revealed

lower rates of PLDKT in Egypt than those in the literature.

CONCLUSION

Patient age, sex, and primary kidney disease are independent predictors of achieving living donor KT. Despite its non-significant effect, PAKT may enhance the low rates of PLDKT. The main causes of non-achievement of PLDKT were patient regression on starting regular dialysis and donor unavailability or exclusion.

Key Words: Access to kidney transplantation; Donor regression; Kidney transplantation; Living donors; Preemptive kidney transplantation; Transplantation

Core Tip: Patients with preemptive access to kidney transplantation (PAKT) may have significant differences from those with conventional access to KT, warranting more evaluation. In this study, known primary kidney disease was an independent factor of achievement of living donor KT (LDKT). In addition, the older age and female sex were independent predictors of non-achievement of LDKT. However, unavailability, regression, and exclusion of LDs and patient regression on starting dialysis may prevent achievement of preemptive LDKT (PLDKT) in patients with PAKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The current literature review may refer to that PLDKT has comparable or variably better outcomes than the conventional LDKT. Hence, PLDKT is recommended as the first choice for each candidate patient. In Egypt, the rate of PLDKT is still lower than that of other countries, warranting implementation of effective strategies to promote PLDKT.

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INTRODUCTION

Preemptive kidney transplantation (PKT) is defined as receiving kidney transplantation (KT) before initiation of maintenance dialysis in patients with end-stage renal disease (ESRD)[1,2]. This definition may vary from one KT program to another, where patients who receive dialysis sessions sporadically or as conditioning pre-transplantation sessions for no more than 1 wk may be included in this definition[2-6]. The evolution of PKT was more than 30 years ago[7], when it passed through an insidious course and gained variably insufficient interests among the physicians and surgeons in the KT community[1,5]. Many initiatives and programs have been triggered to promote PKT, especially in the sector of living donor kidney transplantation (LDKT). These initiatives promote living kidney donation (LKD) programs as the most effective contributor to PKT[4-7]. PKT is a time-based KT strategy controlled by setting the timing of KT surgery at a point just before the start of regular dialysis as much as possible. This philosophy represents the natural course of management of most diseases. However, it has generated debate along the different axes of KT, such as the proposed lead-time bias effect on the outcomes of PKT[8]. The incidence of PKT has improved gradually from 2% in its early years to 6%-7% in the last years. Most cases come from LDKT programs, where it may reach up to 34% in some countries that adopt LDKT programs[6,9]. The latter percentage refers to the fundamental role of LD in the promotion of PKT strategy[10]. Preemptive access to KT (PAKT) and waitlisting are other effective contributors to PKT. Hence, they are fundamental issues in PKT literature[1,11]. However, they have mostly been ignored in research from Egypt, where only LDKT is performed in adults[9,12-14] and pediatrics[15-17].

We assessed the percentage of patients with PAKT and their fate regarding the receipt of preemptive LDKT (PLDKT).

MATERIALS AND METHODS

Study design

A retrospective review was performed for the electronic and manual records of patients with ESRD who sought LDKT in our center from November 2015 to November 2022. The study included both patients with PAKT, which was defined as the presentation of a patient with chronic kidney disease (CKD) stage 4 or 5 for KT prior to the start of regular dialysis and those with conventional access to KT (CAKT). The exclusion criterion was patients who refused KT before starting the preparation for LDKT (Figure 1). The relevant demographic characteristics of the patients and potential donors including age, sex, and relatedness to the potential donors were reviewed. Also, the clinical data including the primary kidney disease, estimated glomerular filtration rate (eGFR) at presentation, outcomes of preparation to KT, causes of deferring LDKT, and fate of the patients and donors were studied. We used the CKD-Epidemiology Collaboration creatinine equation to estimate eGFR for patients with PAKT[18].

Also, a review of the literature was performed to assess PLDKT in KT studies from Egypt. The KT center volume, pre-KT characteristics, and percentages and outcomes of PLDKT were reviewed. Furthermore, the literature was reviewed for the incidence of PLDKT in studies from other countries and large-volume KT registries.

This study was conducted as a topic in a KT research project regarding the outcomes of LDKT at our center. The institutional review board number is 17200148/2017.

Statistical analysis

Statistical analyses were performed with EasyMedStat (version 3.21.4; www.easymedstat.com). Continuous variables are presented as the mean ± standard deviation and range. However, categorical variables are presented as the number and percentage of each category. We created two groups (PAKT and CAKT) according to the status of dialysis at the time of access to transplantation. Normality and hetereoskedasticity of continuous data were assessed with the White test (or with Shapiro-Wilk in multivariate analysis) and Levene's test, respectively. Continuous outcomes were compared with the unpaired Student *t*-test, Welch *t*-test, or Mann-Whitney *U* test according to the data distribution. Categorical outcomes were compared with the chi-squared or Fisher's exact test accordingly. Multivariate logistic regression was performed to assess the factors contributing to achievement of KT in our center. Data were checked for multicollinearity with the Belsley-Kuh-Welsch technique. $P < 0.05$ was considered statistically significant.

RESULTS

Between November 2015 and November 2022, 325 patients attended our center for KT. Twenty-one (6.5%) patients changed their mind or were not serious in accessing KT. The remaining 304 patients were differentiated into PAKT and CAKT groups (Figure 1). The former group included 32 patients (10.5%) who were not on dialysis at the time of access to KT and the latter group included 272 (89.5%) patients with a mean (range) duration of hemodialysis of 6.3 ± 10.5 (0.5–108) mo. Both groups were compared for their demographic and clinical characteristics (Table 1). Follow-up after regression or exclusion decision varied from 3 mo to 6 years.

In the PAKT group, 29 patients (90.6%) failed to receive PLDKT due to original donor unavailability (25%), exclusion (28.6%), regression (3.6%), financial causes (3.6%), and patients' regression from KT when starting regular dialysis (39.3%) (Table 1). Hence, PLDKT was carried out in 3 patients only, representing 5.1% of the total KTs and 9.4% of patients with PAKT. One of these three patients died from complications of the coronavirus disease 2019, 6 mo after KT. The other 2 patients were still living with a functioning graft for 68 and 12 mo at the time of writing of this article. The detailed characteristics of patients with PAKT are presented as individual patients (Table 2). The mean (range) age was 31.7 ± 13 (13-60) years. Most of the patients presented with stage 5 CKD. The mean (range) for serum creatinine level and eGFR was 6 ± 1.6 (3.2–9.8) mg/dL and 12.8 ± 4.8 (7–28) mL/min/1.73 m^2, respectively.

In the current cohort of patients, the total number of patients who had been transplanted at our center (59 patients) or at other centers (29 patients) was 88 (28.9%) patients. In a comparison between the patients who achieved (59 patients) and those who failed to achieve (245 patients) LDKT in our center, there were significant differences in age ($P = 0.034$), sex ($P < 0.001$), primary kidney disease ($P = 0.008$), number of potential donors ($P = 0.003$), and acceptance/exclusion rate of evaluated donors ($P < 0.001$) per patient (Table 3).

In multivariate analysis, known primary kidney disease ($P = 0.002$) was associated with higher rates of achievement of KT in our center. In addition, female sex ($P = 0.001$) and older patients ($P = 0.031$) were significantly associated with lower rates of achievement of KT in our center. However, PAKT ($P = 0.065$) and multiple potential donors ($P = 0.529$) were not significantly associated with the rate of achievement of KT in our center (Table 4).

Table 1 A comparison of the demographic and clinical characteristics of the patients with preemptive access to kidney transplantation and those with conventional access to kidney transplantation, *n* (%)

Variables	PAKT, *n* = 32	CAKT, *n* = 272	*P* value
Age in yr, mean ± SD (range)	31.7 ± 13 (13-60)	32.1 ± 11.5 (12-66)	0.677
Sex			
Men	22 (68.8)	213 (78.3)	0.263
Women	10 (31.2)	59 (21.7)	
Primary kidney disease			
Glomerulonephritis	3 (9.4)	8 (2.9)	< 0.001
Hereditary disease	3 (9.4)	6 (2.2)	
Obstructive uropathy	4 (12.5)	8 (2.9)	
Systemic disease	4 (12.5)	14 (5.2)	
Urolithiasis	3 (9.4)	7 (2.6)	
Unknown	15 (46.9)	229 (84.2)	
Number of potential donors[1]			
Patients presented without donors	8 (25)	36 (13.2)	0.088
With one donor	17 (53.1)	187 (68.8)	
With two donors	4 (12.5)	40 (14.7)	
With three donors	3 (9.4)	9 (3.3)	
Donor evaluation	24	236	
Patients with evaluated donors	20	194	
With accepted donor(s)	10 (50)	89 (45.9)	0.232
With one donor excluded	7 (35)	75 (38.7)	
With two donors excluded	0 (0)	15 (7.7)	
With three donors excluded	1 (5)	2 (1)	
With excluded and accepted donors	2 (10)	13 (6.7)	
Number of not evaluated donors per patient	6	56	
One donor	3 (50)	51 (91.1)	0.024
Two donors	3 (50)	4 (7.1)	
Three donors	0 (0)	1 (1.8)	
Order of the accepted donor	12	102	
First	10 (83.3)	87 (85.3)	0.634
Second	1 (8.3)	11 (10.8)	
Third	1 (8.3)	4 (3.9)	
Accepted donor age (yr), mean ± SD (range)	38.1 ± 9 (25-53)	40.6 ± 10.4 (21-60)	0.39
Patient-donor relatedness degree			
First	5 (41.7)	55 (53.9)	0.234
Second	5 (41.7)	40 (39.2)	
Third	1 (8.3)	6 (5.9)	
Unrelated	1 (8.3)	1 (1)	
Sex of accepted donors			
Women	7 (58.3)	66 (64.7)	0.754
Men	5 (41.7)	36 (35.3)	

Accepted donor commitment			
Donated	4 (33.3)	55 (53.9)	0.171
Regressed	1 (8.3)	16 (15.7)	
Released	7 (58.3)	31 (30.4)	
Number of excluded donors per patient			
One donor	7 (77.8)	84 (80)	0.262
Two donors	1 (11.1)	19 (18.1)	
Three donors	1 (11.1)	2 (1.9)	
Main causes of donor exclusion			
Medical causes	1 (10)	51 (51.5)	0.027
Immunologic mismatch	7 (70)	34 (34.3)	
Combined medical and immunologic	2 (20)	14 (14.1)	
Main causes of donor release	5	28	
Financial causes	0 (0)	3 (10.7)	0.235
Patient death	0 (0)	3 (10.7)	
Patient non-candidacy	0 (0)	10 (35.7)	
Patient regression	5 (100)	12 (42.9)	
Achievement of kidney transplantation			
Failed	25 (78.1)	191 (70.2)	0.568
Transplanted in our center	4 (12.5)	55 (20.2)	
Transplanted in another center	3 (9.4)	26 (9.6)	
Cause of non-achievement of transplantation in our center	28	191	
Donor exclusion	8 (28.6)	88 (40.6)	0.035
Donor regression	1 (3.6)	16 (7.4)	
Donor unavailability	7 (25)	37 (17.1)	
Financial causes	1 (3.6)	13 (5.6)	
Patient non-candidacy	0 (0)	25 (11.5)	
Patient death	0 (0)	5 (2.6)	
Patient regression	11 (39.3)	33 (15.2)	
Fate of recipients who failed to have transplantation in our center			
Death	0 (0)	13 (6)	0.213
On hemodialysis	24 (85.7)	147 (67.7)	
Transplantation in another center	3 (10.7)	26 (12)	
Unknown	1 (3.6)	31 (14.3)	

[1]The headings of the donor evaluation and non-evaluation may include overlapping numbers due to different outcomes of the evaluation of multiple donors, resulting in non-complementary values relative to the total number of patients in both groups.
CAKT: Conventional access to kidney transplantation; PAKT: Preemptive access to kidney transplantation; SD: Standard deviation.

Review of the literature for PLDKT in studies from Egypt revealed that only eight articles addressed PLDKT (Table 5). These articles were from three academic centers only, including seven original research and one opinion article. The percentage of PLDKT varied between 6.4% in adults and 23% in pediatrics. No articles addressed the PAKT or waitlisting. The reported patient and graft survival rates were similar to those of conventional LDKT (CLDKT) in the literature.

In addition, a review of the English literature for the incidence of PLDKT in other countries revealed higher rates than those from Egypt. However, they reported on PKT from both LDs and deceased donors. There were higher rates of PKT in patients who received LDKT than in those who received deceased donor KT (Table 6). In 1987, Migliori *et al*[19] were the first to evaluate the effects and

Table 2 Detailed characteristics and fate of patients with preemptive access to kidney transplantation, *n* = 32

Case Number	Age in yr	Sex	No. of Potential donors relatedness	Primary kidney disease	Serum creatinine in mg/dL	Stage of CKD, eGFR as mL/min/1.73 m^2	PLDKT receipt	Cause of cancelled PLDKT	Fate of the patient
Case 1	48	Male	3 (Wife, Sister, daughter)	Unknown	8.5	5 (7)	None	Donor exclusion	On HD for 20 m then CLDKT in our center
Case 2	25	Male	1 (Mother)	CMU	5.5	5 (14)	None	Donor exclusion	On HD for 62 m
Case 3	28	Male	3 (Brothers)	Unknown	8.2	5 (8)	None	Patient regression	On HD for 74 m
Case 4	59	Female	2 (Sons)	Diabetic nephropathy	5.4	5 (11)	None	Patient regression	On HD 75 m
Case 5	47	Male	2 (Unrelated)	ADPCKD	4.8	5 (14)	Yes	NA	Living with a functioning graft for 68 m
Case 6	26	Male	1 (Brother)	Urolithiasis	7.8	5 (9)	None	Patient regression	On HD then lost to follow up
Case 7	27	Male	1 (Aunt)	Unknown	6.9	5 (10)	None	Patient regression	On HD then CLDKT in another center
Case 8	38	Male	1 (Unrelated)	ADPCKD	7.4	5 (9)	None	Donor exclusion	On HD for 34 m
Case 9	22	Female	None	Unknown	4.8	5 (12)	None	Donor unavail-ability	On HD for 33 m
Case 10	19	Female	None	Unknown	3.5	4 (19)	None	Donor unavail-ability	On HD for 24 m
Case 11	24	Male	None	GN	4.4	4 (18)	None	Donor unavail-ability	On HD then lost to follow-up
Case 12	13	Male	1 (Mother)	Congenital VURD	4.6	4 (18)	Yes	NA	Died from COVID-19 complications
Case 13	14	Male	1 (Mother)	PUV	5.3	4 (16)	None	Donor exclusion	On HD then CLDKT in another center
Case 14	23	Male	1 (Mother)	Urolithiasis	5.1	5 (15)	None	Patient regression	On HD for 18 m
Case 15	34	Female	1 (Sister)	Unknown	8.6	5 (8)	None	Donor regression	On HD for 6 m before death
Case 16	52	Male	1 (Brother)	ADPCKD	6.2	5 (10)	None	Donor exclusion	On HD for 28 m
Case 17	19	Male	None	VURD	3.2	4 (28)	None	Donor unavail-ability	On HD 24 m
Case 18	36	Male	1 (Sister)	Hypertensive nephropathy	6.8	5 (10)	None	Patient regression	On HD for 26 m
Case 19	34	Male	3 (Unrelated)	ADPCKD	7.5	5 (9)	None	Donor exclusion	On HD for 27 m
Case 20	34	Male	2 (Brother, Sister)	Diabetic nephropathy	8.4	5 (8)	None	Patient regression	On HD for 28 m
Case 21	15	Male	1 (Mother)	Unknown	5.4	5 (15)	None	Donor exclusion	On HD for 6 m then lost to follow-up
Case 22	44	Male	1 (Brother)	Urolithiasis	6.7	5 (10)	None	Patient regression	On HD for 8 m then lost to follow-up
Case 23	40	Female	1 (Cousin)	Unknown	6.7	5 (7)	None	Donor regression	Unknown
Case 24	44	Male	1 (Brother)	Hyperuricemia	5.6	5 (12)	None	Donor exclusion	On HD for 13 m
Case 25	19	Male	1 (Mother)	Congenital	4.7	4 (17)	Yes	NA	Living with a

				VURD					functioning graft for 12 m
Case 26	23	Female	1 (Mother)	Unknown	6.3	5 (12)	None	Patient regression	On HD for 18 m
Case 27	60	Male	None	Unknown	5.6	5 (11)	None	Donor unavailability	On HD then CLDKT in another center
Case 28	29	Male	1 (Sister)	GN	3.9	4 (19)	None	Donor exclusion	On HD 8 m
Case 29	25	Female	1 (Brother)	Unknown	9.8	5 (7)	None	Patient regression	On HD for 6 m
Case 30	47	Female	None	Unknown	6.4	5 (12)	None	Patient regression	On HD for 16 m
Case 31	25	Male	None	FSGS	4.5	4 (18)	None	Donor unavailability	On HD for 5 m
Case 32	21	Female	None	Unknown	4.2	4 (18)	None	Donor unavailability	On HD for 3 m

ADPCKD: Autosomal dominant polycystic kidney disease; CKD: Chronic kidney disease; CLDKT: Conventional living donor kidney transplantation; CMU: Congenital megaureter; COVID-19: Coronavirus disease 2019; eGFR: Estimated glomerular filtration rate; FSGS: Focal segmental glomerulosclerosis; GN: Glomerulonephritis; HD: Hemodialysis; N/A: Not applicable; PLDKT: Preemptive living donor kidney transplantation; PUV: Posterior urethral valve; VURD: Vesicoureteral reflux disease.

outcomes of PKT in a large study from the United States, reporting a PKT rate of 7.6%. They were followed by two European studies with variable rates[20,21]. Then, five studies presented data from registries from United States and Canada and reported higher PKT rates up to 21% of the total KTs and more than 29% of LDKTs[22-26]. In addition, three studies from Japan, Australia, and Korea presented PLDKT rates up to 22% in patients receiving LDKT[27-29]. In 2009, two studies of mixed LD and deceased donor KTs showed higher rates of PLDKT about 39%[30,31]. Between 2011 and 2016, five studies of pediatric and adult KT showed similar rates[2,32-35]. In the last 3 years, many studies have reported high PLDKT rates more than 34%of LDKTs[36-38].

DISCUSSION

We addressed the topic of PKT in Egypt, because there is a question that whether the reported incidence of PLDKT correlates with the international values. Because this question may entail addressing the barriers and the promoting strategies of PLDKT, we performed this retrospective study to assess the outcomes of patients accessed KT at our center. In addition, review of PLDKT publications coming from Egypt was carried out in the context of the international literature, either as specific studies for PLDKT within LDKT cohorts or as combined LDKT and deceased donor KT researches. There is significant variability in the rates of PKT all over the world. In most studies, the proportions of PLDKT are higher than those of PKT in deceased donor KT. Most of these studies showed significantly higher incidences in adults and pediatrics. However, because the total percentages of LDKT are lower than those of KT from deceased donors, the frequency of PKT from deceased donors represented the majority of cases of PKT in some studies. However, relative to the total numbers of donor source, the percentages of PLDKT of total LDKTs are steadily higher than those of PKT from the total deceased donor KTs (Table 6).

In Egypt, there is an obvious lack of research on PKT represented by the small number of studies that was found in this topic[12-16]. These studies were mostly retrospective and presented as few centers' experiences or small cohorts of patients. Hence, the volume of research on PLDKT is relatively small, referring to that PKT does not seem to be in the focus of research. PLDKT has just been mentioned as a category within the total cohorts of KT from centers with well-established KT programs[13,17]. On the other hand, a few studies were specifically conducted to study PLDKT outcomes in comparison to CLDKT[9,12]. This may be a part of the lack in the international literature, which has a slowly propagating body of research on PKT[33,38]. Currently, the literature refers to some sort of practical negligence of PKT in many forms, including disparities in access to PKT among the waitlisted patients. In a study from the United States, relative to the rates of White (38%) and Black (31%) patients on the waiting list, there was a significant difference between the rates of White (65%) and Black (17%) patients who had PKT in 2019[1]. Also, there is a substantially lower rates of PAKT among certain demographic groups that may face challenges in engaging with complex health care systems. Patients with low levels of education and those with physician-dependent choice of KT are other groups with disparities in the access to PKT. Inequities in access to KT require substantial efforts and multiple remedies[1]. Unfortunately, there is no studies have been conducted in Egypt to measure the rates of access to PLDKT so far.

Table 3 A comparison of the variables affecting the achievement (*n* = 59) and non-achievement (*n* = 245) of kidney transplantation in our center, *n* (%)

Variables	Achievement, *n* = 59	Non-achievement, *n* = 245	*P* value
Age in yr, mean ± SD (range)	29 ± 9.9 (13-57)	32.8 ± 11.9 (12-66)	0.034
Sex			
Male	56 (94.9)	179 (73.1)	< 0.001
Female	3 (5.1)	66 (26.9)	
Dialysis status			
Preemptive access	4 (6.8)	28 (11.4)	0.354
On regular dialysis	55 (93.2	217 (88.6)	
Primary kidney disease			
Unknown causes	41 (69.5)	202 (82.4)	0.008
Systemic diseases	3 (5.1)	18 (7.4)	
Renal diseases	15 (25.4)	25 (10.2)	
Number of potential donors per patient[1]			
Donor unavailability	0 (0)	44 (18)	0.003
One donor	43 (72.9)	161 (65.7)	
Two donors	13 (22)	31 (12.6)	
Three donors	3 (5.1)	9 (3.7)	
Outcome of donor evaluation[1]			
Accepted	48 (81.4)	51 (32.9)	< 0.001
Excluded	0 (0)	100 (64.5)	
Excluded and accepted	11 (18.6)	4 (2.6)	
Number of not-evaluated donors per patient[1]			
One donor	4 (100)	51 (86.4)	> 0.999
Two donors	0 (0)	7 (11.9)	
Three donors	0 (0)	1 (1.7)	
Chronological order of accepted donor[1]	*n* = 59	*n* = 55	
First	48 (81.4)	49 (89.1)	0.596
Second	8 (13.6)	4 (7.3)	
Third	3 (5.1)	2 (3.6)	
Age of accepted donors, mean ± SD (range)	40.2 ± 10.9 (21-60)	40.5 ± 9.5 (26-58)	0.937
Degree of relatedness of accepted donors[1]			
First	34 (57.6)	26 (47.3)	0.339
Second	20 (33.9)	25 (45.4)	
Third	3 (5.1)	4 (7.3)	
Unrelated	2 (3.4)	0 (0)	
Sex of accepted donor[1]			
Male	20 (33.9)	21 (38.2)	0.779
Female	39 (66.1)	34 (61.8)	
Number of excluded donors per patient[1]	*n* = 11	*n* = 102	
One donor	8 (72.7)	82 (80.4)	0.572
Two donors	3 (27.3)	17 (16.7)	

Three donors	0 (0)	3 (2.9)	
Main causes of donor exclusion[1]	n = 9	n = 100	
Medical causes	5 (55.6)	47 (47)	0.462
Immunologic mismatches	2 (22.2)	39 (39)	
Combined medical and immunologic causes	2 (22.2)	14 (14)	

[1]The values and percentages of the donors are not complementary to the total number of patients, because there were multiple donors for 56 patients who had overlapping outcomes of evaluation and fate.
SD: Standard deviation.

Table 4 Multivariate logistic regression analysis of the variables influencing the achievement of kidney transplantation in our center

Variables	Modality	Odds ratio	*P* value
Age	Younger *vs* older	0.97 (0.94-0.997)	0.031
Sex	Men *vs* women	0.14 (0.04-0.46)	0.001
Dialysis status	Preemptive *vs* on dialysis	0.31 (0.09-1.1)	0.065
Primary kidney disease	Known *vs* unknown	3.24 (1.5-6.9)	0.002
Number of potential donors	One *vs* multiple	0.81 (0.42–1.57)	0.529

The current study showed that PAKT represented only 10.5% of patients who were referred to KT in our center.

From the reviewed literature, the reported incidence of PLDKT in the different Egyptian KT centers was relatively lower than the international values (Tables 5 and 6). The range was 5%-6% of the total KTs that were performed in these centers[12,13]. However, the incidence was higher, when PLDKT was studied in a certain category of population, such as pediatrics with low-body weight[16,17]. Similarly, the rate of PLDKT was 5.1% in the current study. However, these values are still significantly lower than the values reported in the international literature (Table 6).

Patients with PAKT may have high education levels, payment resources, married status, residence near to KT centers, and younger age than those with CAKT. Unknown primary diseases and glomerulonephritis seemed to be the most common categories of primary kidney disease in adults[9,12,21]. Among pediatrics, reflux nephropathies, nephrotic syndromes, and congenital anomalies are the commonest primary diseases[15,16]. In addition, PLDKT patients had a lower likelihood of testing positive for hepatic viruses and receiving a blood transfusion than the CLDKT patients[12]. Of the 304 patients who accessed LDKT in our center, only 32 patients had PAKT. In turn, only 3 patients succeeded in having PLDKT and they included 2 children and 1 adult patient. They had congenital or hereditary diseases as primary causes of ESRD and the donors were unrelated donor in one case and mothers in the other 2 cases.

A large retrospective study from Mansoura Urology and Nephrology Center studied the course and outcomes of PLDKT and reported an incidence of 6.4%. In addition, it showed that there was only a significant difference in the percentages of patients who died with functioning grafts due to cardiovascular disorders and respiratory infections. The former cause was higher in PLDKT, while the latter was higher in CLDKT[12]. In a smaller prospective comparative study, we found that the incidence of acute graft rejection was significantly higher among early LDKT (ELDKT) patients than in PLDKT patients. However, the incidence of lymphoceles was significantly higher in PLDKT patients than in patients receiving ELDKT[9]. In the current study, the rates of non-candidacy and death during preparation to KT were lower in patients with PAKT (0%) than in patients with CAKT (10.7% and 35.7%, respectively). These rates may be because patients in the former group were healthier than those in the latter group.

The previous characteristic may be a surrogate of the concerns raised about the proposed effect of the lead-time bias on the advantaged outcomes of PLDKT. However, there may be a different perspective, regarding this postulation. We hypothesized that the proposed effects are a mere component of the strategy of PKT. This could simply be explained by considering the PKT and non-PKT as consecutive rather than parallel processes along the course of ESRD. PKT is an early step in the management of ESRD. So, the time factor should be considered a promotor rather than a confounder to PKT process. On the other hand, the idea of removal of the lead-time bias means discarding the spirit of the entire process of PKT[8]. The best support of this perspective is studying the outcomes of KT relative to the time-point at which KT is performed. Goldfarb-Rumyantzev *et al*[39] designed a study based on this idea and it revealed significant survival advantages when KT was performed before 180 d of dialysis.

Table 5 Preemptive living donor kidney transplantation in publications from Egypt

Ref.	Publishing place	Settings	Type	Aim	Scope relative to PLDKT	Target age group	Outcomes relative to ELDKT/ CLDKT	Number of patients; PLDKT/Total (Percentage of PLDKT)
El-Agroudy *et al*[12]	*Transplantation*	Mansoura University	Retrospective comparative	Compare outcomes of CLDKT & PLDKT	Specific	Mixed	Comparable, except in death with functioning graft was due to CVD in PLDKT *vs* respiratory infections in CLDKT	82/1279 (6.4%)
Bakr and Ghoneim[14]	*Saudi J Kidney Dis Transpl*	Mansoura University	Retrospective series	Present experience in KT	General	Mixed	Overall graft survival rates were 76% and 52% at five and 10-yr, respectively	82/1690 (4.9%)
El-Husseini *et al*[15]	*Pediatr Nephrol*	Mansoura University	Retrospective series	Evaluate outcomes of pediatric LDKT	General	Pediatrics	5-yr graft survival was 73.6%	51/216 (23%)
Mosaad *et al* [16]	*Dial Transpl*	Mansoura University	Retrospective series	Study LDKT survival in low-weight children	General	Pediatrics	PLDKT might provide better graft survival	9/63 (14.3%)
Saadi *et al*[13]	*Egyptian J Int Med*	Cairo University	Retrospective series	Identify KT Epidemiology in Cairo University hospitals	General	Mixed	Most of patients and donors were males, mostly as LDKT	14/282 (5%)
[1]Gadelkareem *et al*[9]	*Afr J Urol*	Assiut University	Prospective comparative	Compare short term outcomes of ELDKT & PLDKT	Specific	Adults	Comparable, except AR higher in ELDKT; Lymphocele incidence was higher in PLDKT	PLDKT 30/45; ELDKT 15/45
Gadelkareem *et al*[8]	*Exp Tech Urol Nephrol*	Assiut University	Opinion	Suppose that lead time should not be a bias effect in PKT	Specific	Mixed	Lead time is a mere character of PKT rather than a bias	NA
Fadel *et al*[17]	*Pediatr Transpl*	Cairo University	Retrospective series	Present experience in pediatric KT	General	Pediatrics	Timely referral and parent education were recommended	PLDKT 11/148 (7%); ELDKT 59/148 (40%)
Index study	*World J Nephrol*	Assiut University	Retrospective series	Present experience	Specific	Mixed	Urological causes are main contributor	PLDKT 3/59 (5.1%)

[1]Early living donor kidney transplantation was defined as receiving kidney transplantation within 6 mo from starting regular dialysis.
AR: Acute rejection; CLDKT: Conventional living donor kidney transplantation; CVD: Cardiovascular disease; ELDKT: Early living donor kidney transplantation; KT: Kidney transplantation; LDKT: Living donor kidney transplantation; N/A: Not applicable; PKT: Preemptive kidney transplantation; PLDKT: Preemptive living donor kidney transplantation.

Internationally, many articles have addressed the barriers of PKT. The unavailability of a suitable, willing donor is a major confounder to PLDKT[40-42]. In accordance, the current results revealed that younger age, male sex, and known primary kidney disease of patients accessing KT in our center were independent predictors of achievement of KT after preparation. However, the dialysis status (PAKT *vs* CAKT), number of potential donors, and their acceptance/exclusion rates were not significantly associated with the achievement of KT. The non-significant effect of PAKT may be attributed to the delayed access of the patients with ESRD. Most of our patients with PAKT were in stage 5 CKD and a mean eGFR of 12.8 ± 4.8 mL/min/1.73 m^2, when they first presented to our clinic. This value of eGFR is comparable to the reported values that allow successful PLDKT[33,43], but these patients were not prepared or waitlisted before presentation to the KT unit. Hence, they needed long duration for preparation, which might be, with donor exclusion, the causes of missing the chance of PLDKT. In addition, the delayed access might be attributed to absence of a well-configured waitlisting programs in our country to refer and prepare patients at the suitable stages of ESRD. On the other hand, there are many underlying primary renal diseases that may predispose to a very late presentation of a significant proportion of patients, such as the status of pending dialysis at first discovery of their ESRD[44].

Problems of unavailability of a well-integrated healthcare system that facilitates early detection of CKD patients and timely referral to KT centers should be practically considered. Paradoxically and despite the observable social fear of ESRD, which may progress up to a disease phobia in developing countries[45], there are many patient-related factors that influence early diagnosis and management of

Table 6 Frequency of preemptive living donor kidney transplantation in publications from other countries/registries, *n* (%)

Ref.	Countryand/or Registry	Total KT Number	PKT	LDKT number (Percentage of PLDKT)	PKT per donor type	
					LD	DD
Migliori *et al*[19]	United States	1742	132 (7.6%)	1056 (9.1)	96 (73)	36 (27)
Berthoux *et al*[20]	ERA-EDTA	35348	2545 (7.2)	1097 (73.3)	804 (31.6)	1741 (68.4)
Asderakis *et al*[21]	United Kingdom	1463	161 (11)	118 (19.5)	23 (14)	138 (86)
Papalois *et al*[22]	United States	1849	385 (20.8)	1074 (29.1)	313 (81.3)	72 (18.7)
[1]Mange *et al*[23]	United States; USRDS	8489	1819 (21.4)	1819 (21.4)	1819 (100)	NA
Kasiske *et al*[24]	United States; UNOS	38836	5126 (13.2)	13078 (24)	3145 (61.4)	1981 (38.6)
Gill *et al*[25]	Canada; CORR	40963	5996 (14.6)	11290 (26.6)	2999 (50.5)	2967 (49.5)
Ashby *et al*[26]	United States; OPTN/SRTR	102331	17885 (17.5)	44033 (26.3)	11601 (65)	6284 (35)
[1]Ishikawa *et al*[27]	Japan; JRTR	834	112 (13.4)	834 (13.4)	112 (100)	NA
[1]Milton *et al*[28]	ANZDATA	2603	578 (22)	578 (22)	578 (100)	NA
[1]Yoo *et al*[29]	Korea	499	81 (16.2)	499 (16.2)	81 (100)	NA
Gore *et al*[30]	United States; UNOS	41090	11026 (26.8)	15940 (39.4)	6282 (57)	4744 (43)
Witczak *et al*[31]	Norway	3400	809 (24)	1415 (36.3)	514 (64)	295 (36)
[2]Kramer *et al*[32]	ERA-EDTA	1829	444 (21.2)	1073 (11.5)	123 (72)	321 (28)
Grams *et al*[33]	United States; UNOS	152731	19471 (12.8)	NA	11554 (59)	7917 (41)
[1]Grace *et al*[34]	ANZDATA	4105	660 (16.1)	2058 (16.1)	660 (100)	NA
[2]Patzer *et al*[35]	United States; USRDS	5774	1117 (19.3)	2598 (28.8)	747 (67)	370 (33)
Jay *et al*[2]	United States; UNOS	141254	24609 (17)	46373 (31)	14503 (59)	10106 (41)
Prezelin-Reydit *et al*[36]	France; REIN	22345	3112 (14)	2031 (34)	690 (22.2)	2422 (77.8)
[1]Kim *et al*[37]	South Korea	1984	429 (21.6)	1984 (21.6)	429 (100)	NA
[2]Prezelin-Reydit *et al*[38]	France; REIN	1911	380 (19.8)	240 (37.5)	90 (23.7)	290 (76.3)

[1]Studies included only living donor kidney transplantation.
[2]Studies included only pediatric kidney transplantation.
ANZDATA: Australia and New Zealand Dialysis and Transplant Registry; CORR: Canadian Organ Replacement Registry; DD: Deceased donor; ERA-EDTA: European Renal Association-European Dialysis and Transplant Association; JRTR: Japanese Renal Transplant Registry; LD: Living donor; LDKT: Living donor kidney transplantation; PKT: Preemptive kidney transplantation; PLDKT: Preemptive living donor kidney transplantation; N/A: Not applicable; OPTN/SRTR: Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients; REIN: Renal Epidemiology and Information Network; UNOS: United Network for Organ Sharing; USRDS: United State Renal Data System.

CKD patients such as the cultural and health illiteracies[44]. As a developing country, the healthcare authorities in Egypt have a large burden of challenges which seem hard to be overcome due to factors such as low per-capita income and slowly progressing corrections of the healthcare systems[15]. Also, the ethical problems that have been raised about KT practice in Egypt represent another major confounder to correction[46]. However, the recent policies in the Egyptian national healthcare system seem to be promising as a mass modification to overcome these problems, including the new national health insurance coverage and national KT programs.

The limitations of the current study included the small number of patients who had PLDKT, which made us unable to perform statistical analyses for the independent factors of failure of most patients with PAKT to achieve PLDKT. However, this is the first study from Egypt to address this very viable topic at a national review basis. Hence, it may unmask the vague situation of PLDKT in Egypt by configuring a step forward in building more integrated KT systems.

Based on relevant literature review, we may recommend implementation of different strategies to promote PLDKT in Egypt. Encouragement of LKD is the main strategy that should be extensively studied, because our national KT program is currently devoted to LDKT only. Minimally-invasive approaches such as laparoscopic living donor nephrectomy should be introduced to all centers of KT. Also, the regulations of LKD should be organized under a well-configured national donation program,

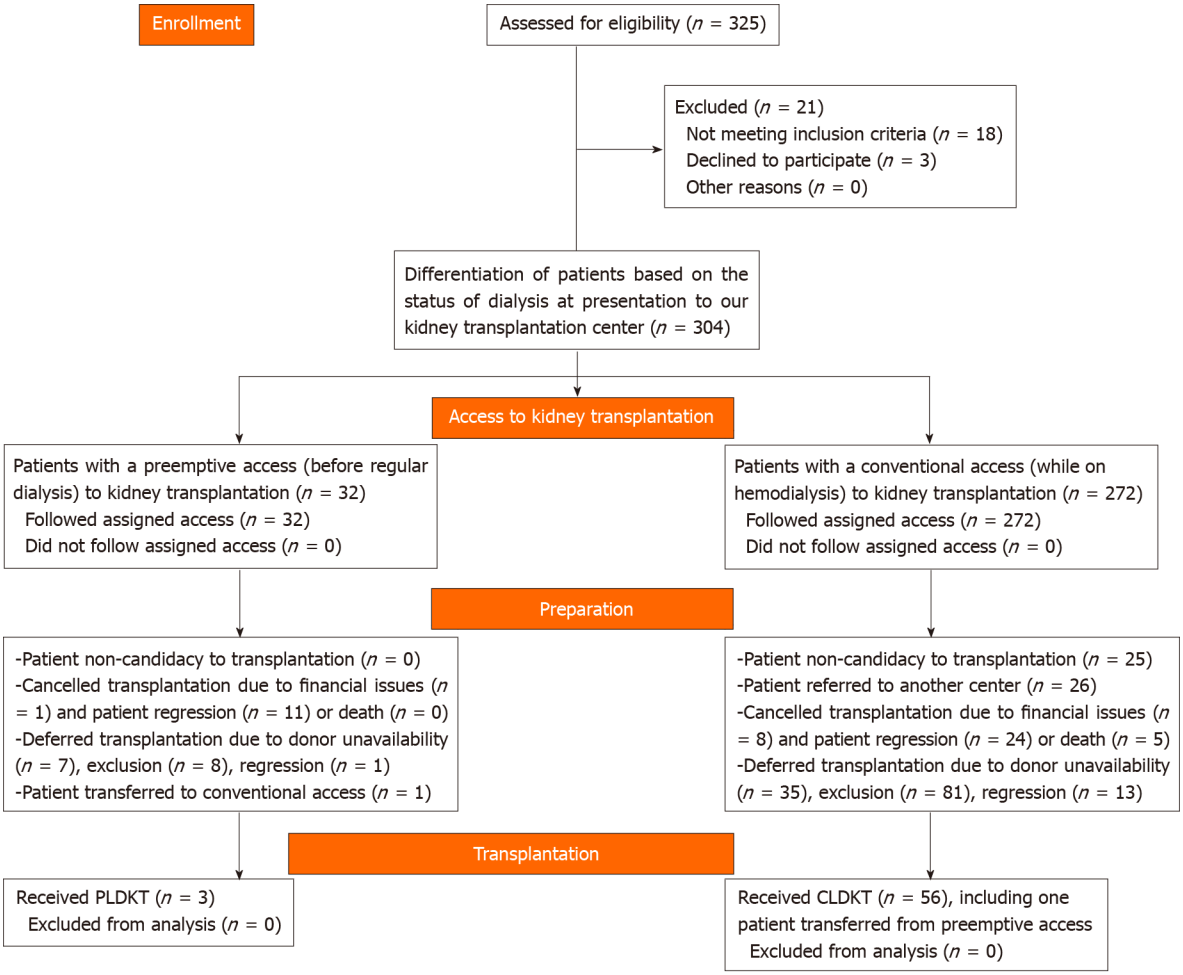

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Figure 1 Flowchart of patients who accessed our center seeking living donor kidney transplantation. Relative to the status of dialysis at access, this chart shows the steps through which the patients and their potential donors were evaluated to achieve kidney transplantation. CLDKT: Conventional living donor kidney transplantation; PLDKT: Preemptive living donor kidney transplantation.

including donor exchange programs. Furthermore, promotion of healthcare facilities of early detection of CKD and education of the contributors of PLDKT process are crucial strategies for this topic. The latter includes the education of the physicians (representing the moderator of the process), ESRD patients (representing the key start of the process), and publics (representing the source of the potential donors) about the benefits of PKT.

CONCLUSION

Patients with PAKT may have significant differences from those with CAKT regarding age, sex, primary kidney disease, and number of potential donors at presentation to a KT center. A primary kidney disease diagnosis is an independent factor of achievement of LDKT. In addition, older age and female sex are independent predictors of non-achievement of LDKT. On the other hand, unavailability, regression, and exclusion of LDs and patient regression when reach dialysis may hinder the achievement of PLDKT in patients with PAKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The current literature review may refer to that PLDKT has comparable or slightly better outcomes than those of CLDKT. Hence, PLDKT is recommended as the first choice for each candidate patient. In Egypt, PLDKT may have similar barriers to those presented elsewhere in the literature, including the shortage of donors, delayed presentation of patients and socioeconomic factors. As a result, the rate of PLDKT is still low in Egypt, warranting implementation of many strategies to promote PLDKT. They include encouraging LKD, introduction of minimally-invasive living donor nephrectomy, configuring a specific program for LKD, and education of the physicians, patients and publics about the benefits of PKT.

ARTICLE HIGHLIGHTS

Research background

Despite its low rates, preemptive living donor kidney transplantation (PLDKT) is recommended as the optimal treatment for end-stage renal disease. However, its rate is still lower than the expected rates worldwide.

Research motivation

Promotion of the rate of PLDKT seems to be a modifiable variable for improvement of the total outcomes of KT.

Research objectives

To assess the rate of achievement of PLDKT among patients accessing KT in our center and to review the status of PLDKT in Egypt in the context of the international literature.

Research methods

We performed a retrospective review of the records of patients who accessed KT in our center from November 2015 to November 2022. The demographic and clinical characteristics of the patients and their potential donors were reviewed. Also, the literature was reviewed for PLDKT status in Egypt.

Research results

Of 304 patients accessed KT, 32 patients (10.5%) had preemptive access to KT (PAKT). The means of age and estimated glomerular filtration rate were 31.7 ± 13 years and 12.8 ± 3.5 mL/min/1.73 m^2, respectively. Fifty-nine patients had KT, including three PLDKTs only (5.1% of the total KTs and 9.4% of PAKT). Twenty-nine patients (90.6%) failed to receive PLDKT due to donor unavailability (25%), exclusion (28.6%), regression from donation (3.6%), and patient regression on starting dialysis (39.3%). In multivariate analysis, known primary kidney disease (P = 0.002), patient age (P = 0.031) and sex (P = 0.001) were independent predictors of achievement of KT in our center. However, PAKT was not significantly (P = 0.065) associated with the achievement of KT. Review of the literature revealed lower rates of PLDKT in Egypt, including the current results, than the internationally reported rates.

Research conclusions

Patient age, sex, and primary kidney disease are independent predictors of achieving LDKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The main causes of non-achievement of PLDKT were patient regression on starting regular dialysis and donor unavailability or exclusion.

Research perspectives

Studying the factors that may promote the early access of ESRD patients to KT may improve the rates of PLDKT. This latter strategy may improve the whole outcomes of the process of KT, including avoidance of the inconveniences of dialysis and improvement of the graft and patient survival rates.

FOOTNOTES

Author contributions: Gadelkareem RA, Abdelgawad AM, and Zarzour MA designed the research, collected the data, and wrote the paper; Reda A, Azoz NM, and Mohammed N contributed to the statistical analysis, literature review, writing and revision; Hammouda HM and Khalil M contributed to the literature review, writing, revision and supervision of the work; All authors approved the paper.

Institutional review board statement: This study has been approved in 2017 by the Medical Ethics Committee of the Faculty of Medicine, Assiut University, Egypt as a topic in a research project titled "Outcome of living donor kidney transplantation in Assiut Urology and Nephrology Hospital". The institutional review board number is 17200148.

Informed consent statement: This article is a retrospective study. Patients were not required to give informed consent to the study because the manipulated data were anonymous and were obtained after each patient agreed to treatment by consent.

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Data sharing statement: The data supporting this study are available from the corresponding author on reasonable request.

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SYSTEMATIC REVIEWS

Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise

Hiroshi Tamura

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Abstract

BACKGROUND

There are two known types of exercise-induced acute renal failure. One is the long-known myoglobinuria-induced acute renal failure due to severe rhabdomyolysis, and the other is the recently recognized non-myoglobinuria-induced acute renal failure with mild rhabdomyolysis. Exercise-induced acute renal failure was first reported in 1982. Non-myoglobinuria-induced acute renal failure is associated with severe low back pain and patchy renal vasoconstriction, and it is termed post-exercise acute renal failure because it usually occurs hours after exercise. It is also called acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE).

AIM

To makes a significant contribution to medical literature as it presents a study that investigated a not-widely-known type of exercise-induced acute renal failure known as ALPE.

METHODS

We performed a database search selecting papers published in the English or Japanese language. A database search was lastly accessed on September 1, 2022. The results of this study were compared with those reported in other case series.

RESULTS

The study evaluated renal hypouricemia as a key risk factor of ALPE. The development of ALPE is due to the sum of risk factors such as exercise, hypouricemia, nonsteroidal anti-inflammatory drugs, vasopressors, and dehydration.

CONCLUSION

In conclusion, hypouricemia plays a key role in the development of ALPE and is often associated with anaerobic exercise. The development of ALPE is a result of the cumulative effects of risk factors such as exercise, hypouricemia, NSAIDs, vasopressors, and dehydration.

Key Words: Acute kidney injury; Exercise; Vasoconstriction; Renal hypouricemia

Core Tip: Exercise is important for health maintenance and promotion. However, exercise-induced acute renal failure is a disease that athletes and doctors should be aware of. This paper makes a significant contribution to medical literature as it presents a study that investigated a not-widely-known type of exercise-induced acute renal failure known as Acute renal failure with severe Loin pain and Patchy renal ischemia after anaerobic Exercise (ALPE). Further, the study evaluated renal hypouricemia as a key risk factor of ALPE. The information in this paper can help clinicians make more accurate diagnosis, given that a significant proportion of patients with ALPE are undiagnosed. Further, this paper can increase awareness among athletes to help them prevent ALPE and reach their exercise goals.

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INTRODUCTION

There are two known types of exercise-induced acute renal failure (ARF). One is the long-known myoglobinuria-induced ARF due to severe rhabdomyolysis, and the other is the recently recognized non-myoglobinuria-induced ARF with mild rhabdomyolysis. The distinguishing features of the two types of exercise-induced ARF are summarized in Table 1.

Exercise-induced ARF was first reported by Ishikawa in 1982. Non-myoglobinuria-induced ARF is associated with severe low back pain and patchy renal vasoconstriction, and it is termed post-exercise ARF because it usually occurs hours after exercise. It is also known as ARF with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE)[1].

Recently, many reports of post-exercise ARF, especially in patients with renal hypouricemia, have attracted attention. Thus, in this study, we report on the types of ALPE.

MATERIALS AND METHODS

Clinical findings in patients with ALPE

We searched PubMed for studies on ALPE and summarized 57 reported cases of ALPE, including self-examination cases[2-29] (Figure 1). The following patient characteristics were investigated: Sex, age at ARF episode, past history, first symptom of the ARF episode, type of exercise leading to ARF, date of ARF episode, first examination data of the ARF episode, baseline levels of uric acid, and treatment of ARF.

Comparison of the characteristics of patients with ALPE

The results of this study were compared with those reported in other case series[30,31].

Comparison of the characteristics of patients with ALPE with and without renal hypouricemia

We compared the characteristics of patients with ALPE and renal hypouricemia with those of patients with ALPE without renal hypouricemia.

Interstudy comparison of the characteristics of patients with ALPE

The characteristics of patients with ALPE with and without renal hypouricemia were compared with those reported in other case series[32].

RESULTS

Clinical findings in patients with ALPE

We summarized 57 reported cases of ALPE, including self-examination cases (Table 2). ALPE most

Table 1 Differential diagnosis of acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise and myoglobinuria acute renal failure

	ALPE	Myoglobinuria acute renal failure
Amount of exercise	+	+++
Type of exercise	Anaerobic exercise	Aerobic exercise
Urine volume	Non-oliguria	Oliguria
Reddish brown urine	-	+++
Loin pain	+++	-~+
Nausea, vomiting/slight fever	++	+-
Dehydration	+	+++
Serum CK/serum myoglobin	normal or mildly elevated	↑↑↑

ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; CK: Creatinine kinase.

Table 2 Clinical findings in 57 patients with acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise, *n* (%)

Age (yr)	22.09 ± 9.55 (13-65)
Sex	Male 52 (91.2%), female 5 (8.8%)
Exercise	47/57 (82.5)
Fever	19/57 (33.3)
Nausea/vomiting	36/57 (63.2)
Loin pain	36/57 (63.2)
Abdominal pain	32/57 (56.1)
High blood pressure on admission	10/30 (33.3)
High CRP on admission	13/18 (72.2)
Serum creatinine on admission (mg/dL)	4.81 ± 2.25 (1.08-12.1), n = 56
Serum myoglobin on admission (ng/mL)	86.46 ± 66.80 (10-260), n = 21
Serum CK on admission (IU/L)	272.76 ± 301.97 (38-1182), n = 47
Kidney CT patchy findings	32/40 (80)
Hemodialysis	10/54 (18.5)
Hydration	37/54 (68.5)
Hydration+drugs	6/54 (11.1) [furosemide (2), dopamine (2), nicardipine (1), Vitamin C, E (1)]
Rest	1/54 (1.9)
Renal hypouricemia	31/57 (54.4)
Recurrence of ALPE	14/54 (25.9)
Days of renal failure improvement	17.4 ± 10.4 (d), n = 35
Premedication	5/26 (19) [vasopressor (2), NSAIDs (1), Antibiotic agent (1), epileptic drugs (1)]

Values are expressed with mean ± standard deviation with (range) or the number of positive cases with (percent). ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; CRP: C-reactive protein; CK: Creatinine kinase; CT: Computed Tomography; NSAIDs: Non-steroidal anti-inflammatory drugs.

commonly occurs post-exercise (82.5%) and in men (91.2%). In addition to back pain (63.2%) at the first hospital visit, many patients with ALPE present with abdominal pain (56%), vomiting (63.2%), mild fever (33.3%), and high C-reactive protein (CRP) levels (72.2%).

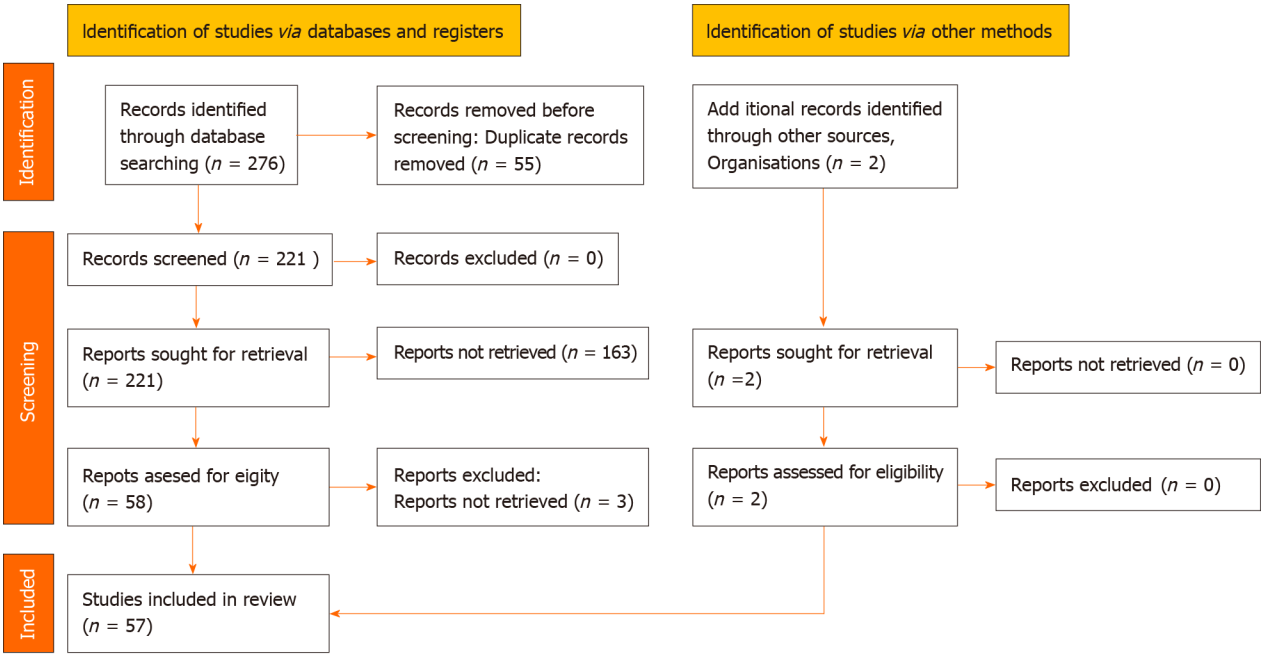

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Figure 1 PRISMA flow diagram.

Wedge-shaped scars were noted on contrast-enhanced computed tomography (CT) in 80% of the cases. The mean serum creatinine, creatine phosphokinase, and myoglobin levels at initial presentation were 4.81 mg/dL, 272 IU/L, and 86 ng/mL, respectively. Moreover, most of the patients (68.5%) only received hydration therapy, 18.5% of the patients underwent hemodialysis (HD), and only a few patients were treated with oral medications. The mean recovery period was approximately 17 d, 25.9% of the patients had ALPE recurrence, and 54.4% of the patients presented with hypouricemia.

Comparison of the characteristics of patients with ALPE

The results of this study were comparable with those of the other case series (Table 3).

Comparison of the characteristics of patients with ALPE with and without renal hypouricemia

Table 4 shows the comparison of the characteristics of patients with ALPE with and without renal hypouricemia. The mean duration of acute kidney injury with hypouricemia was 17.9 d, whereas that of acute kidney injury without hypouricemia was 16.1 d. Overall, 24% of patients underwent HD, 12% of whom did not have hypouricemia. ALPE recurrence with hypouricemia was observed in 39% of patients and that without hypouricemia in 12% of the patients.

Interstudy comparison of the characteristics of patients with ALPE

The findings of this study were consistent with those of previous studies (Table 5).

DISCUSSION

Clinical features of ALPE

The clinical features of ALPE are as follows[33]: ARF (A), severe back (loin) pain (L), and patchy renal ischemia of acute onset (P) after anaerobic exercise (E). Most patients with ALPE (approximately 90%) are men, and the age of onset is as low as 15-17 years. Most cases have been reported so far in Japan, and the relationship between ALPE and renal hypouricemia has attracted attention. Some patients administered antipyretic analgesics before exercise and had a slight cold. The risk factors for ALPE are summarized below.

Exercise: The types of exercises include anaerobic and repeated anaerobic exercises, such as track and field (sprinting), soccer, muscle training, swimming, cycling, baseball, and weightlifting. ALPE most commonly occurs after sprinting 200 m multiple times at sports festivals[34].

Loin pain: Loin pain refers to severe pain that seems to originate from the kidney, rather than from the muscles of the extremity used during exercise. It occurs 1–48 h (typically 3-12 h) after exercise. The pain is bilateral and mostly described as back pain, but it is occasionally described as abdominal, low back, or

Table 3 Comparison of characteristics in acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise, *n* (%)

	This cases	Ohta *et al*[31], 2004	Ishikawa *et al*[30], 2002
Age (yr)	22.1 ± 9.6 (13-65)	19.3 ± 8.1 (11-46)	22.0 ± 7.6 (10-54)
Sex (male)	52/57 (91.2)	48/54 (88.9)	112/118 (94.9)
Fever	19/57 (33.3)	7/60 (11.7)	38/47 (80.9)
Nausea/vomiting	36/57 (63.2)	51/60 (85)	84/88 (95.5)
Loin pain	36/57 (63.2)	35/60 (58.3)	NA
Abdominal pain	32/57 (56.1)	22/60 (36.7)	NA
Serum creatinine on admission (mg/dL)	4.81 ± 2.52 (N = 56)	NA	4.70 ± 2.90 (N = 77)
Kidney CT patchy findings	32/40 (80)	NA	49/96 (92)
Hemodialysis	10/54 (18.5)	NA	20/118 (16.9)
Exercise	47/57 (82.5)	61/61 (100)	118/118 (100)
Renal hypouricemia	31/57 (54.4)	48/48 (100)	49/96 (51)
Recurrence of ALPE	14/54 (25.9)	13/54 (24.1)	20/118 (16.9)
Days of renal failure improvement	17.4 ± 10.4 (N = 35)	NA	13.1 ± 8.3 (N = 87)

Values are expressed with mean ± standard deviation with (range) or the number of positive cases with (percent). ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; CT: Computed Tomography; N: Number of patients; NA: Not available.

flank pain.

High pain severity does not allow patients with loin pain to drive a car. In addition, the patients complain of nausea, vomiting, and abdominal pain. They present to the hospital with mild fever and slightly high CRP levels.

Renal hypouricemia: Patients with ALPE and renal hypouricemia typically have more frequent relapses, more severe ARF, and longer recovery periods than those with ALPE and no renal hypouricemia. Since the identification of the gene for renal hypouricemia in Japan[35], post-exercise ARF has been gaining popularity as a complication of renal hypouricemia.

Clinically misdiagnosed diseases: ALPE may include clinically misdiagnosed diseases, such as urinary tract stones, acute gastroenteritis, acute pancreatitis, acute glomerulonephritis, acute pyelonephritis, and lumbago.

Diagnostic method: Having sufficient knowledge of ALPE is the first step in its diagnosis. A considerable number of ALPE cases may remain undiagnosed and are overlooked. It is important to obtain a medical history of exercise, especially anaerobic exercise, for accurate diagnosis of ALPE.

Diagnostic criteria

(1) History of repeated anaerobic exercise or exercise set that includes anaerobic exercise; (2) Back pain experienced 1-48 h (typically 3–12 h) after exercise; (3) Normal or slightly elevated serum creatine kinase (CK) levels (serum CK levels that are ≤ 9 times the reference value and serum myoglobin levels that are ≤ 7 times the reference value); and (4) Wedge-shaped residual contrast medium observed on delayed CT (1–2 d after the administration of the contrast medium) when the serum creatinine level is 1.2-3.5 mg/dL. ARF with criteria (1) to (3) is required for the diagnosis of ALPE; however, criterion (4) is not required for clinical diagnosis[33]. In rare cases, patients do not complain of back pain or remember exercising. These cases are considered atypical.

In atypical cases of ALPE, urinalysis does not show reddish-brown urine, patients usually have nonoliguric ARF, and oliguria is rare. The level of fractional excretion of sodium fluctuates between < 1% and > 1%. Furthermore, proteinuria and hematuria may be positive or negative, and the result of urinalysis is not definitive. Dehydration is rare, and the blood pressure level at the time of admission is usually normal.

Treatment: A considerable number of patients with low back pain several days after a sports festival may be overlooked without a diagnosis of ALPE who ultimately heal spontaneously. If a patient with ALPE presents to an emergency department with pain, nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered without consideration. This is because NSAIDs may exacerbate ARF,

Table 4 Comparison of characteristics in acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise with and without renal hypouricemia, *n* (%)

	Renal hypouricemia	No renal hypouricemia
Number of patients	31	26
Age (yr)	21.6 ± 10.7 (11-65)	22.7 ± 8.0 (13-49)
Sex (male)	28/31 (90)	24/26 (92)
fever	7/31 (23)	12/26 (46)
Nausea/vomiting	22/31 (71)	14/26 (54)
Loin pain	21/31 (68)	15/26 (58)
Abdominal pain	14/31 (45)	18/26 (69)
High blood pressure on admission	6/21 (28.6)	4/9 (44.4)
High CRP on admission	9/14 (64.3)	4/4 (100)
Serum creatinine on admission (mg/dL)	4.53 ± 2.04 (N = 30)	5.24 ± 2.81 (N = 26)
Serum CK on admission (IU/L)	261 ± 304 (N = 26)	269 ± 225 (N = 21)
Kidney CT patchy findings	9/15 (60)	23/25 (92)
Hemodialysis	7/29 (24)	2/25 (8)
Exercise	29/31 (94)	19/26 (73)
Recurrence of ALPE	11/28 (39)	3/26 (12)
Days of renal failure improvement	17.9 ± 8.3 (N = 26)	16.1 ± 15.3 (N = 10)
premedication	2/20 (10)	3/6 (50)

Values are expressed with mean ± standard deviation with (range) or the number of positive cases with (percent). ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; CRP: C-reactive protein; CK: Creatinine kinase, CT: Computed Tomography; N: Number of patients.

Table 5 Comparison of characteristics in acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise with and without renal hypouricemia, *n* (%)

	Renal hypouricemia, this cases	Renal hypouricemia, Ishikawa[32], 2014	No renal hypouricemia, this cases	No renal hypouricemia, Ishikawa[32], 2014
Number of patients	31	148	26	94
Age (yr) median	18 (11-65)	18 (15-25)	21 (13-49)	19 (16-26)
Sex (male)	28/31 (90)	136/148 (92)	24/26 (92)	82/92 (89)
Fever	7/31 (23)	35/43 (81)	12/26 (46)	35/49 (71)
Nausea/vomiting	22/31 (71)	106/107 (99)	14/26 (54)	63/66 (95)
Serum CK on admission (IU/L)	155 (44-1182), N = 26	212 (100-447), N = 81	225 (38-686), N = 21	317 (124-696), N = 70
Serum creatinine on admission (mg/dL)	4.2 (1.1-8.9), N = 30	4.3 (2.6-6.7), N = 122	4.7 (1.4-7.6), N = 26	3.2 (2-5.1), N = 75
Kidney CT patchy findings	9/15 (60)	31/32 (97)	23/25 (92)	56/58 (97)
Hemodialysis	7/29 (24)	46/148 (31)	2/25 (8)	16/94 (17)
Recurrence of ALPE	11/28 (39)	38/148 (26)	3/26 (12)	7/94 (7)
Days of renal failure improvement (d)	17 (6-30), N = 26	14 (10-19), N = 85	15 (5-22), N = 10	10 (7-16), N = 66

Values are expressed with median with (range) or the number of positive cases with (percent). ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; CK: Creatinine kinase; CT: Computed Tomography; N: Number of patients.

leading to oliguria and the need for dialysis therapy. If analgesia is considered necessary, centrally administered analgesics should be used instead of NSAIDs. The treatment is initially conservative. Hydration should be normal, and body weight should be maintained at the presymptomatic value. Regarding fluid balance, body weight should be controlled to the standard value with fluid replacement in cases of dehydration, and diuretics should be administered in cases of excess body fluid. Dialysis therapy is rarely used for treating oliguria, uremia, hyperkalemia, and heart failure.

Prevention: The management of patients with renal hypouricemia (particularly those with serum uric acid levels of ≤ 1 mg/dL) is an issue at school club activities and sports festivals. As ALPE recurs easily, patients with a history of ALPE should be advised to be wary of dehydration and of types of exercise likely to induce ALPE. These patients should also be advised to take preventive steps such as avoiding exercises that induce ALPE. However, there is yet no established definitive prevention method against ALPE recurrence. There is insufficient evidence to prove that drugs suppressing the generation of reactive oxygen species, such as allopurinol and vitamins A, C, and E, prevent ALPE[1].

Pathogenesis of ALPE

The pathophysiological mechanism of ALPE is unknown, but renal circulatory impairment due to reactive oxygen species (ROS) is believed to be the main cause of ALPE[36].

Strenuous exercise, such as anaerobic exercise, generates large amounts of ROS, which are rapidly cleared by uric acid, a potent ROS scavenger, and other scavengers in healthy populations[37]. Consequently, patients with renal hypouricemia have insufficient scavengers, leading to inadequate ROS clearance, resulting in the activation of vasoconstrictors, vasoconstriction, and renal ischemia[31].

As renal vasoconstriction is known to cause further vasoconstriction and oxidative stress *via* the activation of the renin–angiotensin system as well as increased blood pressure level[38], patients with ALPE may be in a vicious cycle of oxidative stress and vasoconstriction. Oxidative stress causes stronger vasoconstriction, which in turn causes more oxidative stress, leading to acute ischemia and severe renal damage. The ischemia is localized to the kidney, but on rare occasions, it spreads to other organs. In extremely rare cases, it is accompanied by a spasm of the cerebral vessels, resulting in reversible occipital lobe leukoencephalopathy[39].

Genetic abnormalities in patients with renal hypouricemia who develop ALPE include mutations in the uric acid transporter *URAT1*, homozygotes for W258X, and compound heterozygotes including URAT1 and W258X. Homozygotes for R90H have also been reported[40].

Based on these findings, hypouricemia, rather than genetic mutation, is considered a risk factor for ALPE. In fact, patients with renal hypouricemia are approximately 50 times more likely to develop ALPE than those with nonrenal hypouricemia[32].

The case of a patient with ALPE without exercise who had no episodes of strenuous exercise was recently reported by Lee *et al*[29] However, enhanced CT revealed characteristic patchy renal signs.

To the best of our knowledge, 10 patients with ALPE without an episode of strenuous exercise have been reported so far, 8 of whom had an infection or took a vasopressor or analgesic before the onset of ALPE. Moreover, infection and vasopressor and analgesic use are considered as risk factors for ALPE (Table 6)[3,12,28,31].

The abovementioned reports suggest that ALPE can develop without strenuous exercise or other risk factors.

Aomura *et al*[3] reported ALPE in a patient who took vasopressors for orthostatic dysregulation for 15 days before the onset of ALPE.

It is possible that vasopressors induced or exacerbated ALPE by increasing ROS levels, worsening vasoconstriction, and forming a vicious cycle of decreased renal hemodynamics.

Karasawa *et al*[17] reported the case of a patient who was administered the vasoconstrictor midodrine before the onset of ALPE.

Radaković *et al*[41] demonstrated that vasodilation with low-dose dopamine improved the renal arteriolar resistance index in two cases of ALPE, suggesting a relationship between vasopressors and ALPE in clinical settings.

No study has directly addressed the relationship between vasopressors and ALPE; however, previous studies have shown the importance of catecholamine level homeostasis in the pathogenesis of ALPE. Vasopressors may be associated with the development of ALPE in patients with hypouricemia and may be a risk factor for ALPE.

CONCLUSION

In conclusion, hypouricemia plays a key role in the development of ALPE and is often associated with anaerobic exercise. The development of ALPE is a result of the cumulative effects of risk factors such as exercise, hypouricemia, NSAIDs, vasopressors, and dehydration.

Table 6 Clinical findings of current and previous reported cases of acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise without strenuous exercise

Patient No.	Age (yr)	Sex	Renal hypouricemia	Suspected trigger
1	14	Male	Yes	Gastroenteritis
2	30	Male	Yes	NA
3	33	Male	NR	URI and heavy alcoholconsumption
4	23	Female	NR	URI
5	25	Male	No	URI
6	32	Male	No	NSAIDs
7	30	Male	NR	NA
8	49	Male	Yes	Coincidence of myalgia
9	15	Male	Yes	Vasopressor
10	65	Male	Yes	Ureteral stone and NSAIDs

ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; NA: Not available; URI: Upper respiratory infection; NSAIDs: Non-steroidal anti-inflammatory drugs.

ARTICLE HIGHLIGHTS

Research background

Recently, many reports of post-exercise acute renal failure, especially in patients with renal hypouricemia, have attracted attention. The pathophysiological mechanism of acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE) is unknown, but renal circulatory impairment due to reactive oxygen species is believed to be the main cause of ALPE. Hypouricemia plays a key role in the development of ALPE and is often associated with anaerobic exercise.

Research motivation

Exercise is important for health maintenance and promotion. However, exercise-induced acute renal failure is a disease that athletes and doctors should be aware of.

Research objectives

This paper makes a significant contribution to medical literature as it presents a study that investigated a not-widely-known type of exercise-induced acute renal failure known as ALPE.

Research methods

We performed a database search selecting papers published in the English or Japanese language. A database search was lastly accessed on 1 September 2022. The results of this study were compared with those reported in other case series.

Research results

The study evaluated renal hypouricemia as a key risk factor of ALPE. The development of ALPE is due to the sum of risk factors such as exercise, hypouricemia, nonsteroidal anti-inflammatory drugs, vasopressors, and dehydration.

Research conclusions

Hypouricemia plays a key role in the development of ALPE and is often associated with anaerobic exercise. The development of ALPE is a result of the cumulative effects of risk factors such as exercise, hypouricemia, NSAIDs, vasopressors, and dehydration.

Research perspectives

The information in this paper can help clinicians make more accurate diagnosis, given that a significant proportion of patients with ALPE are undiagnosed. Further, this paper can increase awareness among athletes to help them prevent ALPE and reach their exercise goals.

FOOTNOTES

Author contributions: Tamura H wrote the paper and collected the data.

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CASE REPORT

Infection related membranoproliferative glomerulonephritis secondary to anaplasmosis: A case report

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Abstract

BACKGROUND

Anaplasmosis is a tick-borne disease with a range of clinical manifestations, from a flu-like illness with fever and myalgias to a severe systemic disease with multisystem organ failure. Although renal involvement is not a common presentation, there have been few cases reporting acute kidney injury from Anaplasmosis.

CASE SUMMARY

We present a 55-year-old female with anaplasmosis who developed acute kidney injury due to membranoproliferative glomerulonephritis (MPGN). The patient originally presented with cough and shortness of breath. She was admitted to the hospital with a diagnosis of community acquired pneumonia and received antibiotics. During the hospital course she developed severe acute renal failure. Initial serological work up didn't provide any conclusive diagnosis. Hence, she underwent kidney biopsy which showed MPGN pattern suggesting autoimmune, multiple myeloma or infectious etiology. Extensive work up was undertaken which was negative for autoimmune diseases, vasculitis panel, paraproteinemias but tested positive for IgG anaplasma with high titers indicating Anaplasmosis.

CONCLUSION

Our case shows a unique presentation of severe acute renal failure from MPGN from tick borne illness. MPGN is usually seen with autoimmune diseases, hepatitis C virus infections, paraproteinemias. Hence, we suggest that tick borne illness should also be considered when evaluating acute renal failure cases in tick borne prevalent regions.

Key Words: Acute kidney injury; Membranoproliferative glomerulonephritis; Tick-borne; Anaplasmosis; Case report

Core Tip: In areas endemic for tick borne illnesses, it is important to learn and understand common and rare presentations of tick borne illness. Our case is unique as it showed that tick borne illness can also cause severe renal failure by inciting Glomerulonephritis which is usually seen with other etiologies but very rarely with Anaplasmosis.

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INTRODUCTION

Human granulocytic anaplasmosis (HGA) is a tickborne rickettsial disease caused by the bacterium Anaplasma phagocytophilum. It is a gram-negative intracellular bacterium transmitted by Ixodes scapularis tick. Typical symptoms of HGA include fever, malaise, headache, myalgias, and occasionally arthralgias[1]. We report a case that presented with cough, shortness of breath and acute kidney injury. Only 17 of the 110 reported patients of anaplasmosis had acute kidney injury[1]. To the best of our knowledge, this is the first report of a membranoproliferative glomerulonephritis (MPGN) nephritic pattern of acute kidney injury seen in a HGA infection.

CASE PRESENTATION

Chief complaints

A 55-year-old female presented to the Emergency Department with cough and shortness of breath that had persisted for three days.

History of past illness

The patients' medical history was pertinent for liver cirrhosis secondary to alcohol abuse, ascites requiring weekly paracentesis, chronic hyponatremia secondary to cirrhosis, chronic antibiotics for spontaneous bacterial peritonitis prophylaxis, and hypertension.

Physical examination

After evaluation, there was a concern for pneumonia, based on the basic laboratory tests and a chest x-ray. Her initial vitals were: 104 beats per minute heart rate, 28 per minute respiratory rate, 36.5 degrees Celsius temperature, 128/63 mmHg blood pressure, and 92%SpO2 on presentation to the emergency department. A complete physical examination revealed only significant rales in the left lower lung.

Laboratory examinations

Her coronavirus disease 2019 polymerase chain reaction (PCR) resulted negative (Tables 1 and 2).

Imaging examinations

Chest x-ray showed bilateral patchy opacities and a subsequent computed tomography (CT) scan was performed, revealing pneumonia-like findings.

FINAL DIAGNOSIS

MPGN secondary to Anaplasmosis.

Table 1 Summary of key diagnostic tests

Diagnostic Test	Normal value	Result
ANA	Negative	Negative
Serum DNA double-stranded antibody, IgG	< 30.0 (Negative) IU/mL	< 12.3
Glomerular basement membrane IgG antibody	< 1.0 (Negative) U	< 0.2
Serum myeloperoxidase antibody	< 0.4 (Negative) U	< 0.2
Serum proteinase 3 antibody (PR3)	< 0.4 (Negative) U	< 0.2
Serum complement C3	75-175 mg/dL	42
Serum complement C4	14-40 mg/dL	8
Serum haptoglobin	30-200 mg/dL	17
Serum kappa free light chain	0.3300-1.94 mg/dL	9.28
Serum lambda free light chain	0.5700-2.63 mg/dL	10.9
Kappa/lambda FLC ratio	0.2600-1.65	0.8514
Serum protein electrophoresis	Negative monoclonal proteins	Negative monoclonal proteins
Serum antistrep-O titer	0-530 IU/mL	69
Blood culture	Negative	Negative
Urine culture	Negative	Negative
SARS-CoV-2, PCR, rapid	Undetected	Undetected
EBV DNA, P	Undetected	Undetected
CMV DNA, P	Undetected	Undetected
Anaplasma phagocytophilum, PCR	Undetected	Undetected
Serum Anaplasma phagocytophilum antibody, IgG	< 1:64 titer	1:512
Ehrlichia chaffeensis, PCR	Negative	Negative
Ehrlichia chaffeensis (HME) antibody, IgG	< 1:64	< 1:64
Bartonella antibody panel, IgG and IgM	Negative	Negative
Serum Blastomyces antibody, EIA	Negative	Negative
Histoplasma antibody	Negative	Negative
HIV -1 Ab Screen, P	Negative	Negative
HIV-1 p24 Ag Screen, P	Negative	Negative
HIV Ag/Ab Screen, P	Negative	Negative
HIV-2 Ab Screen, P	Negative	Negative
Serum Mycoplasma antibody, IgM	Negative	Negative
Serum Mycoplasma antibody, IgG	Negative	Positive
Serum total hepatitis B core antibody	Negative	Negative

HIV: Human immunodeficiency virus; ANA: Serum antinuclear antibody; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; PCR: Polymerase chain reaction; EBV: Epstein–Barr virus; CMV: Cytomegalovirus; FLC: Free light chains.

TREATMENT

She was admitted to the hospital and started on empiric antibiotics for community-acquired pneumonia with cefepime and metronidazole. Her baseline creatinine was 0.6 to 1 mg/dL but during the hospital course she developed an acute kidney injury, with her creatinine reaching 1.6 mg/dL. Her acute kidney injury was thought to be caused by hepatorenal syndrome. She received albumin, midodrine, and octreotide.

Table 2 Laboratory test results

Diagnostic test	Normal value	At presentation	Hospital day 2	Hospital day 6	Hospital day 11	Hospital day 15	On discharge
Hemoglobin, g/dL	11.6-15.0	8.9	8	9.1	9	6.8	7.3
WBC count, $\times 10^9$/L	3.4-9.6	15.5	16.2	16.8	12.6	8.1	9.2
Platelet count, $\times 10^9$/L	157-371	118	105	168	157	115	124
Serum Urea Nitrogen, mg/dL	45098	31	36	55	46	66	87
Serum creatinine, mg/dL	0.59-1.04	1.62	1.84	1.02	1.55	2.87	2.95
Serum sodium	135-145 mmol/L	124	123	129	126	127	135
Serum potassium	3.6-5.2 mmol/L	4.5	4.3	3.7	3.8	3.8	4
Serum chloride	98-107 mmol/L	102	100	105	95	95	100
Serum bicarbonate	22-29 mmol/L	11	11	10	20	20	20
eGFR	≥ 60 mL/min/BSA	35	30	62	37	18	17
Anion gap	45122	11	12	12	9	12	15
Serum calcium	8.6-10.0 mg/dL	7.7	7.3	7.8	7.2	7.3	7.6
Serum albumin	3.5-5.0 g/dL	1.6		1.4	1.8		

WBC: White blood cell; eGFR: Estimated glomerular filtration rate; BSA: Body surface area.

OUTCOME AND FOLLOW-UP

On day 5, she underwent paracentesis due to underlying alcoholic liver cirrhosis with ascites. The paracentesis cultures were negative. On day 6, renal function recovered to baseline, but the leukocyte count remained persistently elevated, despite empirical treatment with cefepime and metronidazole. Her respiratory status did not improve, and a repeat chest CT was performed on day 7, revealing persistent bilateral opacities. Concurrently, her leukocytosis was worsening. Pulmonology was consulted and they have recommended diuresis to relieve the fluid overload and also recommended getting an echocardiogram. Her echocardiogram showed severe pulmonary hypertension, mild mitral regurgitation, and an ejection fraction of 60% without regional wall motion abnormalities.

During her hospital course, she developed anemia, with her hemoglobin dropping from 9 g/dL on day six to 6.8 g/dL on day fifteen. She was then transfused with two packed red blood cell (pRBC) units. The anemia evaluation revealed low haptoglobin, elevated lactate dehydrogenase, and a negative Coombs test. Peripheral blood smears lacked schistocytes but indicated that the patient had chronic normocytic anemia with elevated polychromasia in circulating nucleated erythrocytes.

Her renal function deteriorated again on day 11 with creatinine rising gradually to 2.9 mg/dL. Urinalysis revealed 11-20 white blood cell (WBC) per high-power field, more than 100 RBC, and a protein level of over 300, with a urine protein-to-creatinine ratio of 1.45. Serologies and a kidney biopsy were requested due to concerns over glomerulonephritis. Anti-neutrophil cytoplasmic antibody, serum protein electrophoresis, serum-free light chains, cryoglobulins, Anti streptolysin O antibody, and *Legionella* urine antigen tests were negative. Her serum C3 and C4 complement levels were both low, likely due to liver failure.

A kidney biopsy was performed. The biopsy revealed a MPGN pattern of injury. Immunofluorescence showed granular capillary wall deposits of IgA, IgG, and IgM, as well as C1q, kappa light chain, and lambda light chain, which are characteristic of immune-complex mediated MPGN with polyclonal deposits. Additionally, IgG subtype immunofluorescence was performed to exclude a monotypic antibody process. By subtyping, IgG subclasses were polytypic: IgG1, IgG2, and IgG3 were positive, and IgG4 was negative. By electron microscopy, the mesangial and peripheral capillary wall deposits were reiterated, but these electron-dense deposits showed an unusual fibrillary substructure (Figure 1). The differential diagnosis for such an injury pattern included autoimmune diseases, atypical infections, and hematologic processes, such as cryoglobulinemia. There was no evidence of an underlying autoimmune diseases, paraproteinemia, or cryoglobulinemia after a comprehensive evaluation.

As all her autoimmune tests and monoclonal protein studies came back negative, it was suggested that she should undergo a thorough investigation into infectious etiology. A repeat workup with urine cultures, blood cultures, human immunodeficiency virus (HIV) testing, viral hepatitis panel, Histoplasma antibodies, Blastomyces antibodies, Bartonella antibodies, and PCR for Epstein–Barr virus

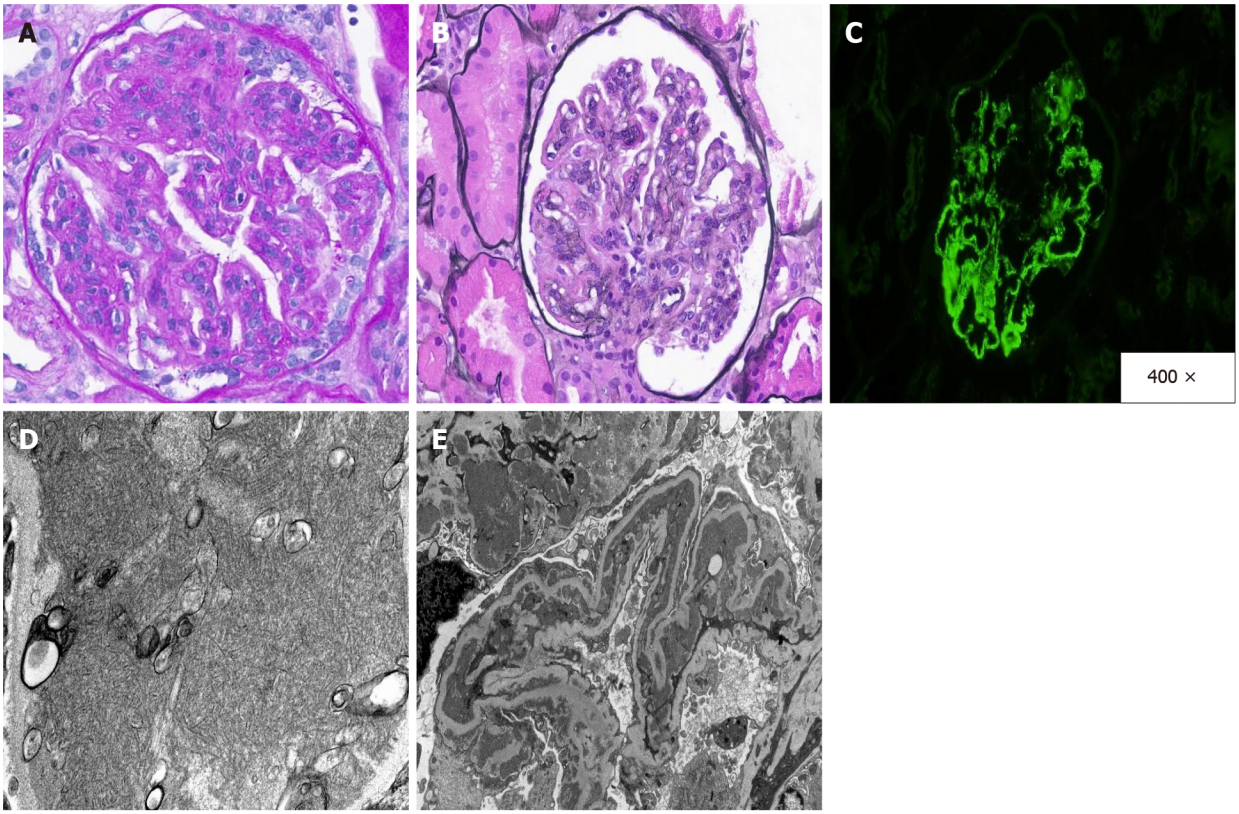

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Figure 1 Kidney Biopsy. A: Light microscopy sections show enlarged glomeruli with lobular accentuation of the capillary loops and both mesangial and endocapillary hypercellularity [periodic acid-Schiff (PAS), 400 ×]; B: Silver-negative, PAS-positive deposits are seen along the capillary loops, resulting in extensive capillary wall remodeling (Jones methenamine silver, 400 ×); C: These deposits show a full-house pattern, highlighting with all immunoglobins and complement components on both standard and pronase immunofluorescence studies (IgG, 400 ×); D and E: On electron microscopy, numerous organized, electron-dense deposits with fibrillary substructure are seen within the mesangial and peripheral capillary loop walls [E: Electron microscopy (EM), 6000 ×], including focal areas with stacked parallel arrays are seen (D: EM, 50000 ×).

(EBV), Cytomegalovirus (CMV), Anaplasma, Methicillin-resistant *Staphylococcus aureus*, and streptococcal urine antigen were all negative. Her echocardiogram was negative for endocarditis. She had elevated Anaplasma antibody titers, IgG 1: 512. Infectious disease was consulted, and they advised starting doxycycline. She was started on doxycycline and was also started simultaneously on pulse steroids and prednisone taper as her kidney biopsy showed edema and inflammation in the renal parenchyma (Table 1).

But her kidney function continued to deteriorate. The patient was informed of the biopsy results and treatment options. She was not in need of dialysis immediately but informed her that she might need it if her renal function continued to worsen. With her other comorbidities, and after discussion, our patient decided to pursue comfort-only measures rather than aggressive treatment options and was discharged to home hospice.

DISCUSSION

Since the first reported case in Wisconsin in 1990, cases of HGA have steadily increased, rising from 348 cases in 2000 to 5655 cases in 2019 with a peak of 5762 cases in 2017. Anaplasmosis is commonly reported in the Upper Midwestern and Northeastern United States. However, only 88 case reports have been published thus far[1].

Tick bites are the most common mode of transmission for Anaplasmosis, mainly Ixodes ticks. The most common symptoms are fever, malaise, myalgias, headache, anorexia, and gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal pain, cough, and occasionally a rash[1,2]. HGA symptoms and presentation are typically nonspecific and may be difficult to distinguish from other infections. Therefore, a high index of suspicion must be maintained. Diseases transmitted by the same vector, such as Lyme disease, Ehrlichiosis, and Babesiosis, are included in the differential diagnosis of Anaplasmosis; however, other zoonoses and non-vector-borne diseases should also be considered. Non-tick-borne infections, such as viral exanthems (human herpesvirus 6, EBV, enterovirus, adenovirus, and parvovirus B 19), and bacterial infections, are still considered in the differential

diagnosis of anaplasmosis (Endocarditis, N. meningitides, N. gonorrhea, and secondary syphilis)[3,4]. Anaplasmosis is a clinical condition, however due to the nonspecific presentation, a broader workup to rule out other tick-borne diseases should be considered. Anaplasmosis causes mild anemia, thrombocytopenia, and leukopenia, as well as a mildly to moderately elevated liver function test[5]. A peripheral blood smear may show morulae within granulocytes, but this is not conclusive. The most conclusive tests are the indirect fluorescent antibody test and the polymerase chain reaction, which show a four-fold increase in IgG-specific antibodies and Anaplasma DNA in a whole blood sample, respectively[1].

Many complications of Anaplasmosis have been reported, which include end-organ damage such as acute kidney injury, rhabdomyolysis[2], multiorgan failure, non-traumatic splenic rupture, pancreatitis, secondary hemophagocytic lymphocytosis, and meningoencephalitis. Anaplasmosis has been linked to kidney disease, which is uncommon. In our case, the patient developed acute kidney injury due to MPGN from Anaplasmosis, which is very rare[6].

In this case, our patient was hospitalized with a diagnosis of community-acquired pneumonia and given antibiotics. During her hospitalization, she developed an acute kidney injury which we suspected was due to hepatorenal syndrome. Her kidney function initially improved with treatment, but it deteriorated again with a nephritic pattern of injury as evidenced by hematuria and proteinuria on urinalysis. In addition, her kidney biopsy revealed an unusual MPGN pattern of injury.

MPGN typically manifests in childhood, though it can manifest at any age. The clinical presentation and progression are extremely variable, ranging from benign to rapidly progressive. Thus, patients may exhibit asymptomatic, acute nephritic syndrome, nephrotic syndrome, or even rapidly progressive glomerulonephritis symptoms. In addition, the degree of kidney impairment varies based on the underlying lesions in the kidney, such that if a kidney biopsy reveals proliferative lesions, one is more likely to have a nephritic phenotype[3]; those with crescentic MPGN may present with rapidly progressive glomerulonephritis; and those with both repair and sclerosis are more likely to have a nephrotic phenotype. The MPGN pattern results from two underlying pathologies: (1) Immune complex-mediated; and (2) Complement-mediated. The immune-complex-mediated MPGN injury pattern is caused by circulating immunoglobulin or immune complexes, and etiologies include monoclonal gammopathy, autoimmune or rheumatologic disease, infection, or idiopathic[3]. This injury pattern is characterized by immune deposits that stain with either IgG or IgM predominance; typically complement staining is present, but not as strong as immunoglobulin staining. By contrast, complement-mediated MPGN—which encompasses C3 glomerulonephritis and dense deposit disease—typically will stain predominately with C3 and will typically have either genetic or acquired complement pathway alterations[3].

Monoclonal processes—such as proliferative glomerulonephritis with monoclonal deposits—can present with an MPGN pattern. However, unlike other immune-complex mediated MPGN, the immune complexes are monoclonal, not polyclonal, though an underlying B-cell/plasma cell clonal process is not always discovered or present[7]. In this case, immunofluorescence tests for both κ and λ light chains were positive, suggesting a polyclonal process. IgG subtype staining also showed polytypic distribution, further corroborating a polyclonal process[7,8]. Additionally, a normal κ:λ ratio and negative serum protein electrophoresis test for monoclonal proteins eliminated the need for a hematologic or oncologic evaluation.

However, infectious causes remained to be identified for MPGN-pattern nephritic renal injury. We performed a thorough infectious workup that included a viral hepatitis panel, Ehrlichia, Bartonella, Blastomyces, Histoplasma, HIV-1 and HIV-2 antibodies and antigens such as p24 and HIV Ag/Ab ratio, Anaplasmosis, Mycoplasma IgM and IgG, ascitic fluid studies, anti-strep-O titers, severe acute respiratory syndrome coronavirus 2, EBV, and CMV. Except for the anaplasmosis antibody, serum IgG 1:512 (normal IgG 1:64), which is 8 times higher than normal, all results were negative. This demonstrates that in our case, anaplasmosis is the underlying cause of the MPGN pattern nephritic etiology. Infectious disease was consulted, and a 14-d course of twice-daily doxycycline was given. She did not require dialysis and was started on high-dose prednisone with stabilization of her creatinine between 3.0 to 3.5 mg/dL and blood urea nitrogen between 130 and 140 mg/dL without significant uremic symptoms. Although she had anasarca, she did not require supplemental oxygen at the time of discharge. To control metabolic acidosis, sodium bicarbonate was added, and sevelamer was used for hyperphosphatemia. However, due to her current medical conditions and poor prognosis, the patient opted for comfort care, and she ultimately passed away.

CONCLUSION

Tick-borne diseases are relatively common, but early detection is essential. Due to obstacles such as the absence of objective, measurable evidence for these symptoms, it is difficult to determine whether a patient's complex of symptoms is the result of tick-borne disease or another cause. Due to these obstacles, there is a greater chance of overlooking tick-borne diseases as an etiology, which can result in complications and poor outcomes. Even though we reached a conclusion in our case and decided to initiate treatment, our patient had transitioned to comfort care measures only and declined further

treatment. Due to the increasing prevalence of renal involvement and other complications in tick-borne diseases, it is crucial to diagnose and treat tick-borne diseases in their earliest and most prevalent stages.

FOOTNOTES

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