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Clinical Characteristics of Acute Appendicitis in Kidney Transplant Recipients

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Background: Clinical characteristics of acute appendicitis in kidney transplant recipients may be different from those in the general population due to kidney transplant recipient's immunosuppressive state and position change of appendix caused by graft.

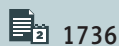
Material/Methods: Clinical characteristics of 10 cases of acute appendicitis among 2880 cases of kidney transplantation were evaluated, including diagnostic rate, location of appendix and complication in kidney transplant recipients.

Results: Acute appendicitis was suspected in 9 of 10 patients (90%) with acute appendicitis based on clinical and laboratory findings. Five patients (50%) presented with typical migrating pain and 1 patient (10%) had only periumbilical pain. Leukocytosis (WBC >10 000) was present in 8 patients (80%). Radiologic study revealed various locations of appendix relative to grafted kidney. Computed tomography scan was superior to ultrasonography in diagnosis of acute appendicitis. The complication rate was 50%. Complicated patients showed longer duration from symptoms onset to operation (69±48 hours versus 25±6 hours, $P<0.05$) and hospital stay (15.4±15 days versus 5.4±1.8 days, $P<0.05$) than uncomplicated patients.

Conclusions: Clinical suspicion and differential diagnosis are needed for kidney transplantation patients with acute appendicitis. Early diagnosis with radiologic study is essential to reduce complications of acute appendicitis.

MeSH Keywords: Appendicitis • Kidney • Transplantation

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Background

Although acute appendicitis is rare in kidney transplant recipients, it is associated with higher complication rate than that in the general population [1,2]. Diagnosis of acute appendicitis in kidney transplant recipients is different from that in the general population because immunosuppressed state of kidney transplant recipients can mask typical symptoms and position change of appendix after kidney transplantation [3]. In addition, other medical problems can make it difficult to diagnosis acute appendicitis in kidney transplant recipients.

Few studies have reported acute appendicitis in kidney transplant recipients. In a study analyzing almost 8000 solid organ transplantations, only 17 patients had undergone appendectomy [4]. Because of its low incidence, acute appendicitis in kidney transplant recipients has been studied in case report [3], or retrospective study with limited clinical information [1,2]. Thus, the objective of this study was to investigate characteristics of acute appendicitis in terms of diagnostic rate, location of appendix, and complication in kidney transplant recipients.

Material and Methods

Medical records of patients who underwent kidney transplantation at Seoul St. Mary's Hospital between March 25, 1969 and December 31, 2017 were reviewed. A total of 2880 cases of kidney transplantation were reviewed, and 10 cases of appendicitis were identified. This study was approved by the Institutional Review Board (IRB) of Seoul St. Mary's Hospital (IRB No. XC15RIMI0072K). The need for an informed consent was waived due to the retrospective nature of this study.

From medical records, we retrieved baseline characteristics including age, gender, information about transplantation, clinical symptoms, and laboratory findings. Computed tomography (CT) scan and ultrasonography were reviewed using a picture archiving and communication system (PACS, INFINIT Co., Seoul, South Korea). Intravenous contrast was used for all patients who received CT scans.

We obtained clinical information, including location of abdominal pain, fever, and gastrointestinal symptom, as key information that could help differential diagnosis. Laboratory tests performed for all patients included white blood cell (WBC) on complete blood count (CBC), serum creatinine, and WBC count on routine urinalysis. C-reactive protein (CRP) was only measured in 4 patients because CRP was usually conducted at our institution only in later years of the study (after 2000s).

We investigated the location of appendix from the view of cecum or from the view of graft kidney based on imaging study

and surgical record. The location the appendix from the view of cecum was expressed as retrocecal, antececal, subcecal, or pelvis. The location the appendix from the view of graft kidney was expressed as upper-side of kidney, medial-side of kidney, or posterior-lateral side of kidney.

To evaluate whether delayed diagnosis or operation affected complication rates, we classified patients into complicated and uncomplicated groups and compared mean duration of pre-hospital time, in-hospital time, and overall time between the 2 groups. We defined pre-hospital time, in-hospital time, and overall time as duration from symptom onset to hospital arrival, from hospital arrival to operation, and from symptom onset to operation, respectively. Complicated appendicitis included perforated appendicitis, appendiceal abscess, and peritonitis. In addition, we evaluated hospital stay between complicated and uncomplicated patients with acute appendicitis.

Descriptive data was expressed as mean standard deviation or median (range). All statistical analyses were performed with Mann-Whitney U test to compare duration from symptom onset to operation and hospital stay between complicated and uncomplicated groups. Statistical significance was considered when *P*-value was less than 0.05.

Results

Baseline characteristics

Demographic and clinical characteristics of the 10 patients with acute appendicitis are presented in Table 1. The prevalence of appendicitis was 0.35% among all kidney transplant recipients. The prevalence of male patients with acute appendicitis was 0.44% and that of female one was 0.17%. Of these 10 patients with acute appendicitis, 8 patients (80%) were males and 9 patients (90%) had living donors. Chronic glomerulonephritis (CGN) was the most common cause of renal failure in 6 patients (60%). All grafts were first transplanted and implanted in right lower quadrant (RLQ). The median time from kidney transplantation to diagnosis of acute appendicitis was 41 months (range, 1–125 months). The median age at diagnosis was 49 years (range, 35–74 years). At the time of diagnosis, all patients received steroid. Nine patients (90%) received calcineurin inhibitor (5 patients received cyclosporin and 4 patients received tacrolimus) while 5 patients (50%) received antimetabolite (4 patients received MMF and 1 patient received azathioprine). Median trough levels of cyclosporin and tacrolimus when visiting the hospital were 107.5 ng/mL (range, 50–233 ng/mL) and 11.9 ng/mL (range, 2.8–25 ng/mL), respectively.

Table 1. Clinical characteristics of 10 patients with acute appendicitis after kidney transplant.

Case	Age/ gender	Immunosuppressant	Clinical findings			Laboratory findings			Differential diagnosis
			Location of abdominal pain	Fever (38°C<)	Nausea/ vomiting	WBC (10 ⁹ /L)	Cr (mg/dl)	CRP (mg/dl)	
1	58/M	AZP + steroid	RLQ	N	N	16.1	1.6	N-A	–
2	74/M	CsA + steroid	RLQ	N	N	18	1.4	N-A	Graft rejection Duodenal perforation
3	49/M	CsA + steroid	RLQ	N	N	17.1	2	N-A	Graft pyelonephritis
4	39/M	FK + steroid	Migrating	N	Y	12.3	1.8	N-A	Graft rejection
5	67/M	CsA + steroid	Migrating	Y	N	9.3	2	N-A	Gastroenteritis
6	49/F	CsA + steroid	Migrating	Y	Y	13.2	1.1	N-A	Graft pyelonephritis
7	44/M	CsA + MMF + steroid	Migrating	N	N	11	0.8	2.8	Diverticulitis
8	58/F	FK + MMF + steroid	Migrating	N	N	19.3	1.3	9.9	–
9	46/M	FK + MMF + steroid	Periumbilical	N	Y	8.7	1.2	3.4	–
10	35/M	FK + MMF + steroid	RLQ	N	N	15.6	1	7	Op. site pain

AZP – azathioprine; CsA – cyclosporine; FK – tacrolimus; MMF – mycophenolate mofetil; RLQ – right lower quadrant; WBC – white blood cell; Cr – creatinine; CRP – C-reactive protein; Op – operation; N-A – not assessed; Y – yes; N – no.

Clinical and laboratory findings

Table 1 shows individual data of clinical and laboratory findings. The most frequent symptom was abdominal pain (100%), followed by migrating pain from periumbilical to RLQ (60%), localized pain to RLQ (40%), and only periumbilical pain (10%). Fever more than 38.0°C of body temperature was present in 20% of patients while nausea/vomiting was present in 30% of patients. Leukocytosis with WBC greater than 10 (10⁹/L) was present in 80% of patients. CRP level was increased in most patients. There was no pyuria in any patient. Based on clinical and laboratory findings, 90% of patients were suspected to have acute appendicitis. However, 7 patients (70%) needed differential diagnosis for graft-related (rejection, pyelonephritis, or operation site pain) or graft-unrelated (perforation of gastrointestinal tract, gastroenteritis or diverticulitis) complications.

Radiologic findings

Imaging study was conducted for 8 patients (80%) with either CT scan (4 patients) or ultrasonography (4 patients). All patients on CT scan and 2 of 4 patients on ultrasonography were diagnosed with appendicitis. One case of acute appendicitis (Case 2) was diagnosed through explorative laparotomy. Figure 1 shows different locations of appendix on CT scan or ultrasonography. We evaluated the location of appendix in 2 ways. First, from the view of cecum, the appendix was located in retrocecal in

6 cases (60%), antececal in 1 case (10%), subcecal in 1 case (10%), and pelvis in 1 case (10%). The remaining 1 case (10%) was not assessed (Figure 2). From the view of graft kidney, the appendix was located in upper-side of graft kidney in 4 cases (40%, Figure 1A, 1B), medial-side of graft kidney in 3 cases (30%, Figure 1C), and posterior-lateral side of graft kidney in 1 case (10%, Figure 1D). The remaining 2 cases (20%) were not assessed.

Complication and clinical outcome

Open appendectomy was conducted in 8 patients (80%). The other 2 patients had a laparoscopic approach because laparoscopic method was used after 2012. The complication rate was 50%. Appendiceal perforation was the most common (50%), followed by peritonitis (40%). There was no death or treatment failure. Table 2 shows individual data of these parameters. Figure 3 shows comparison of complicated and uncomplicated groups. When we evaluated patients with or without complication, the mean duration of pre-hospital time (61±45 hours versus 15±8 hours, $P=0.19$), in-hospital time (14±12 hours versus 9±8 hours, $P=0.84$), and overall time (69±48 hours versus 25±6 hours, * $P<0.05$) were higher in the complicated group than those in the uncomplicated group (Figure 3). Hospital stay was also longer in the complicated group than that in the uncomplicated group (15.4±15 days versus 5.4±1.8 days, * $P<0.05$).

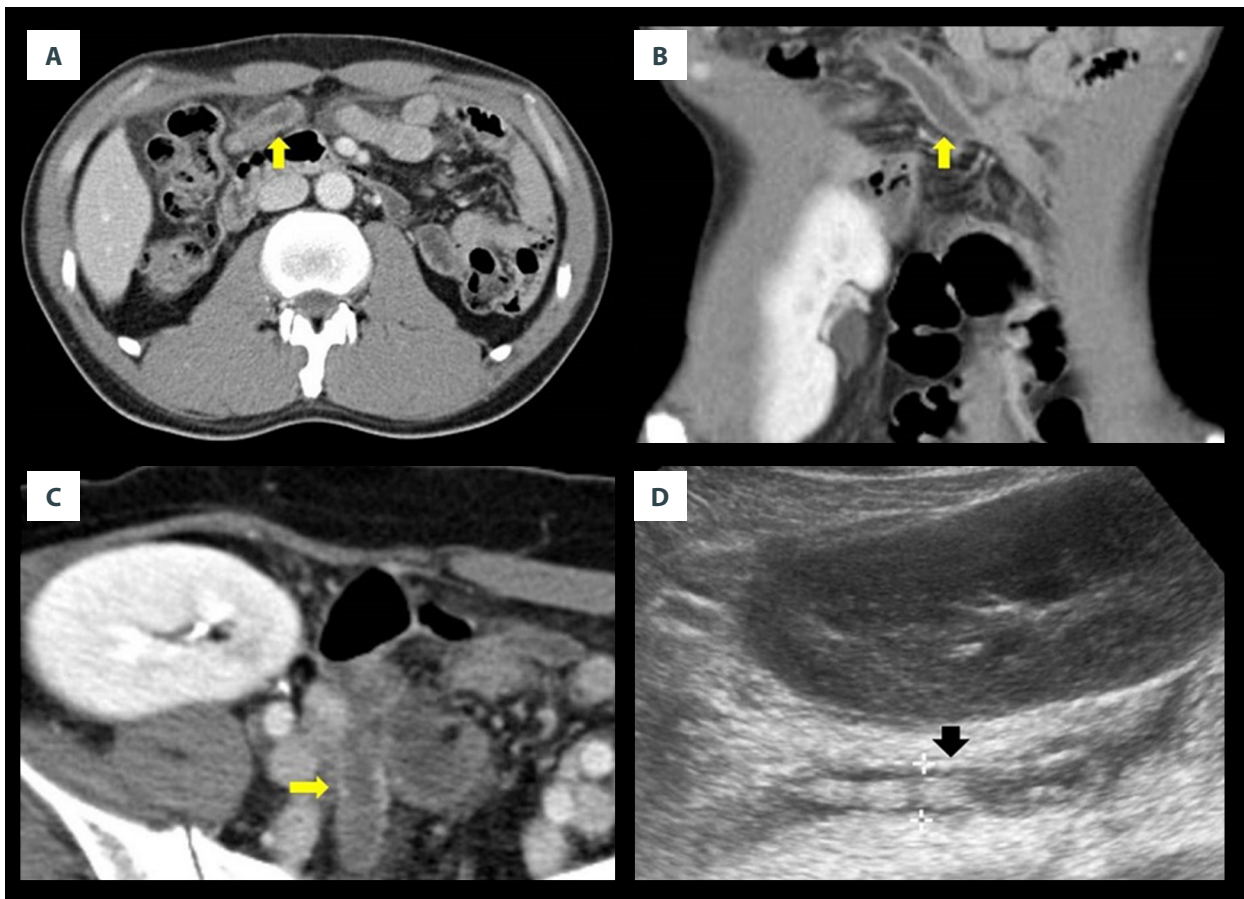


Figure 1. Location of the appendix relative to graft kidney. The appendix located in upper-side of graft kidney (A, B: yellow arrow), medial-side of graft kidney (C: yellow arrow), or posterior-lateral side of graft kidney (D: black arrow).

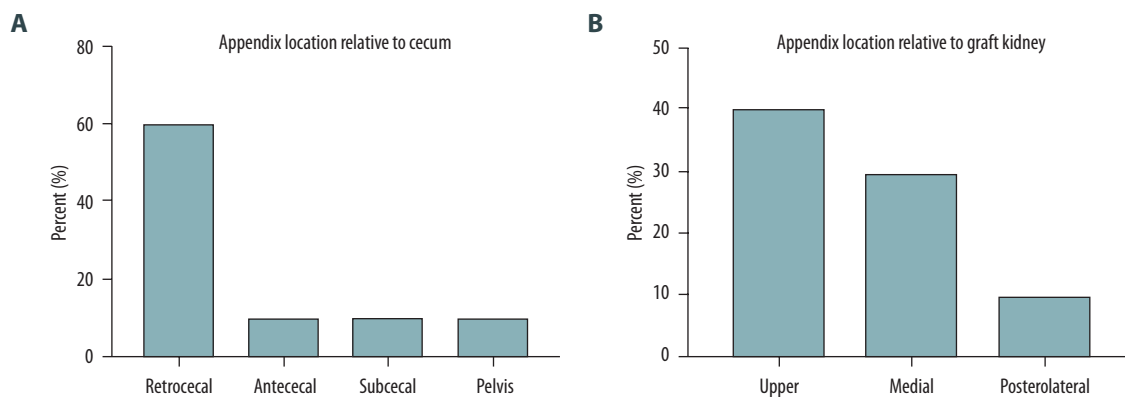


Figure 2. Distribution of anatomical location of appendix. Distribution of anatomical location of appendix relative to cecum (A) and relative to graft kidney (B).

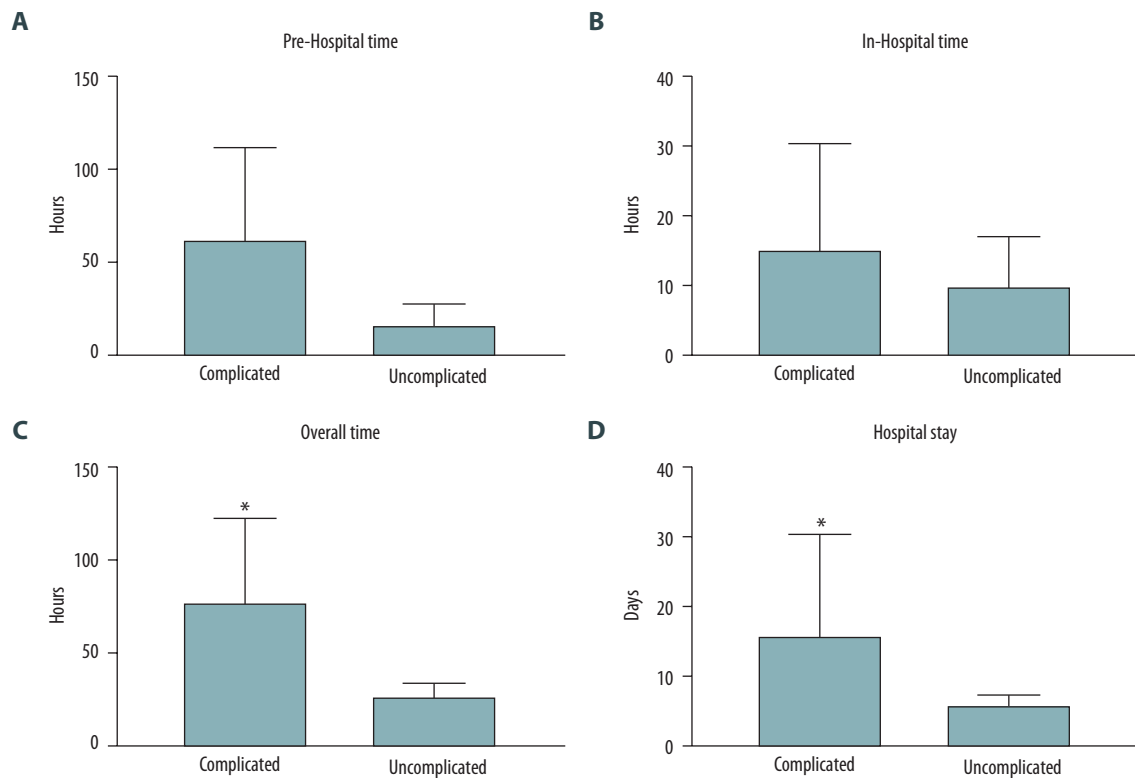
Discussion

Results of our study clearly demonstrate that diagnosis of acute appendicitis in kidney transplant recipients needs not only clinical suspicion, but also radiologic evaluation for investigating

location of appendix and differential diagnosis. Delayed diagnosis can increase complication rate and result in longer hospitalization.

Table 2. Complication according to duration from symptom onset to operation.

Case	Pre-hospital time (hours)	In-hospital time (hours)	Overall time (hours)	Hospital stay (days)	Complication
1	25	1.7	27	5	No
2	120	1	121	42	Appendix perforation, peritonitis
3	96	28	124	10	Appendix perforation, peritonitis
4	10	19	29	8	No
5	14	5.5	20	12	Appendix perforation, peritonitis
6	4	16	20	5	No
7	72	5	77	7	Appendix perforation, peritonitis
8	10	4.3	15	3	No
9	30	7	37	6	No
10	5	35	40	6	Appendix perforation

**Figure 3.** Comparison between complicated group and uncomplicated group. Comparison of mean duration between complicated and uncomplicated groups. Pre-hospital time (A) and in-hospital time (B) had higher tendency in the complicated group. There were significant differences in overall time (C), and hospital stay (D), between the 2 groups. *P*-values were calculated using Mann-Whitney U test and * *P*<0.05 was considered statistically significant.

The diagnosis of acute appendicitis is usually made based on clinical manifestations and laboratory findings. However, the importance of radiological evaluation is increasing. The introduction of abdominal CT scan has decreased the incidence of negative appendectomy from 17% to 2% [5]. In the present study, we suspected acute appendicitis in 9 patients (90%) through clinical and laboratory findings. However, imaging study was needed in 7 patients (70%) for differential diagnosis for graft-related (rejection, pyelonephritis, or operation site pain) or graft-unrelated (perforation of gastrointestinal tract, gastroenteritis or diverticulitis) complications. We performed imaging studies for 8 patients (80%) and found that CT scan was superior to ultrasonography in sensitivity of diagnosis for acute appendicitis (100% versus 50%). All patients who received CT scans with intravenous contrast, but there was no contrast induced nephrotoxicity. Although it remains controversial whether radiological evaluations should be done for all patients with suspected acute appendicitis, our study indicates the importance of radiological evaluation in the differential diagnosis of acute appendicitis in kidney transplant recipients.

Generally, the anatomical position of the appendix is expressed in relation to the cecum and ileum, with retrocecal/retrocolic being the most frequent position (75%) [6]. In this study, kidney transplant recipients showed similar position proportion (retrocecal in 60%). However, the position of the appendix relative to the graft kidney is more important in predicting location of the appendix in kidney transplant recipients because the presence of graft kidney changes the location of appendix. In this study, we found various locations of the appendix relative to the graft kidney (upper or medial, posterior-lateral) as shown Figure 1. Thus, imaging study for acute appendicitis is essential to find the appendix.

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Incidence of appendiceal perforation is generally between 15% and 30% [7]. Perforation rate is increased by 5% per 12-hour period within 36 hours after the onset of symptoms [8]. In addition, in-hospital time delay of more than 12 hours is an independent risk factor for perforation [9]. Our study showed 50% complication rate and that 80% of patients who received their operation more than 36 hour after the onset of symptoms showed appendix perforation. In addition, 50% of patients with in-hospital time delay of more than 12 hours showed appendix perforation. Our findings confirmed previous reports that delayed diagnosis increases complication of acute appendicitis. When we classified patients into complicated and uncomplicated groups, overall time in the complicated group was longer than that in the uncomplicated group as shown in Figure 3. Thus, appendicitis in kidney transplant recipients requires more attention to allow for an early diagnosis, considering the high complication rate in patients with delayed diagnosis.

Limitations of this study include its retrospective nature and the relatively small number of patients. In addition, not all patients in this study had imaging analysis performed. In spite of these limitations, this report provides new findings about the location of the appendix and complications for clinicians to consider.

Conclusions

Early diagnosis of acute appendicitis is essential to decreased complications. When acute appendicitis is suspected, we recommend CT scan to define the location of appendix and make a differential diagnosis of acute appendicitis in kidney transplant recipients.