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## Emphysematous pyelonephritis in a transplanted kidney

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### ABSTRACT

Emphysematous pyelonephritis is a rare infection characterized by necrosis and gas accumulation in the renal parenchyma, adjacent tissues, and/or urinary collecting system. This entity is rarely reported in transplanted kidneys. Computed tomography imaging is necessary for diagnosis and risk classification. The authors described the case of a 58-year-old man who underwent a kidney transplant and presented sepsis from a urinary tract infection. An abdominal tomography showed some characteristics of emphysematous pyelonephritis associated with an abscess. A graft biopsy, performed 45 days after the transplant, failed to show signs of infection, and tubule-interstitial and vascular rejection were ruled out. The patient had a poor outcome, and a nephrectomy was needed, the pathological analysis of which yielded the diagnosis of chronic pyelonephritis with necrotizing papillitis. The patient became hemodynamically unstable and died. The authors highlight the current tomographic criteria for the diagnosis and treatment of emphysematous pyelonephritis and question the validity of accepting the same standards used to guide the treatment of patients without transplants, and call attention to the importance of the clinical status for the indication of nephrectomy in cases of emphysematous pyelonephritis.

### Keywords

Transplantation, Kidney Diseases, Pyelonephritis.

### INTRODUCTION

Emphysematous pyelonephritis (EP) is a rare infectious disease with aggressive clinical behavior, which is observed in patients with diabetes mellitus and is rarely described in transplant recipients whose diagnosis depends on the clinical features and tomographic patterns.<sup>1-4</sup> We report a case of EP in a transplanted kidney, with a discussion of clinical, radiological, therapeutic, and mainly pathological aspects of this disease.

### CASE REPORT

A 58-year-old diabetic man diagnosed with chronic renal failure due to diabetic nephropathy received a deceased donor kidney transplant after 2 years of chronic peritoneal dialysis. The induction immunosuppressive therapy involved thymoglobulin, and the maintenance was held with tacrolimus, mycophenolate sodium, and prednisone. The immediate postoperative period was troublesome, requiring vasoactive drugs and chemical cardioversion for an atrial flutter. The transplant

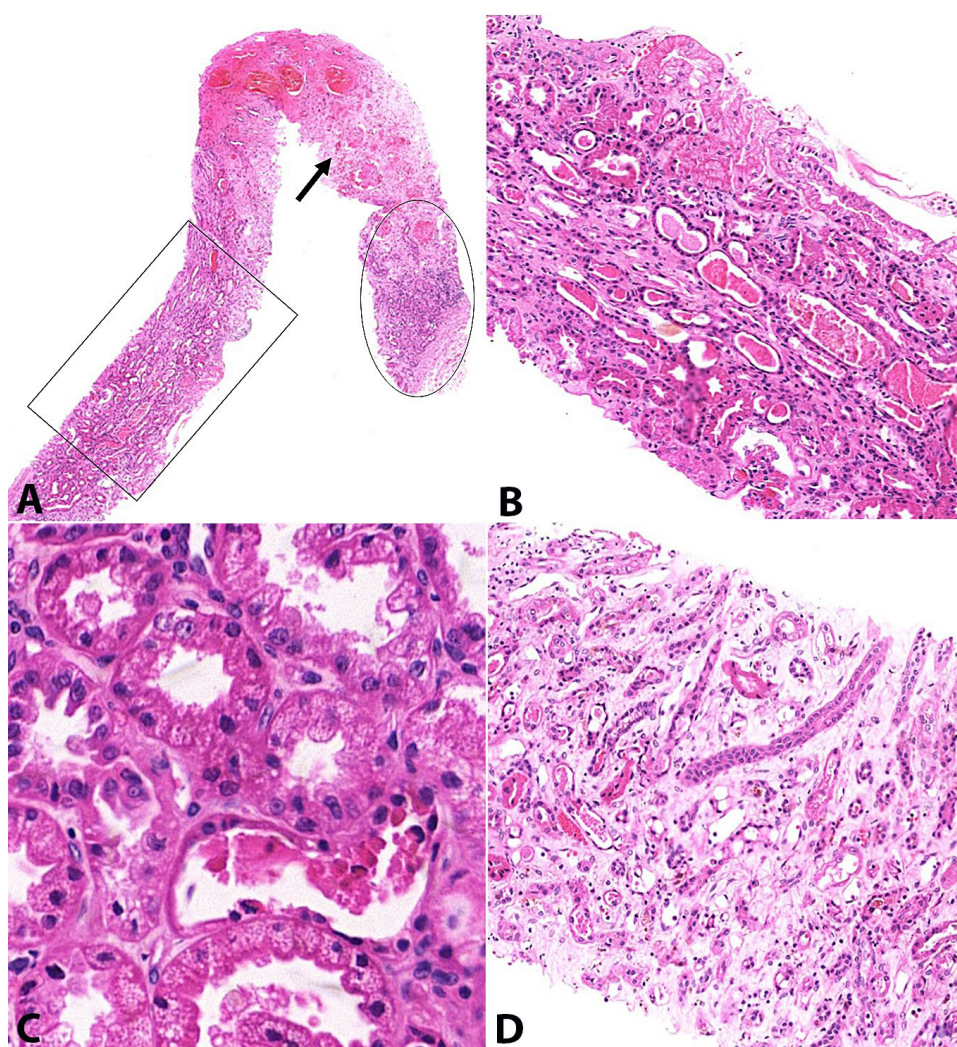
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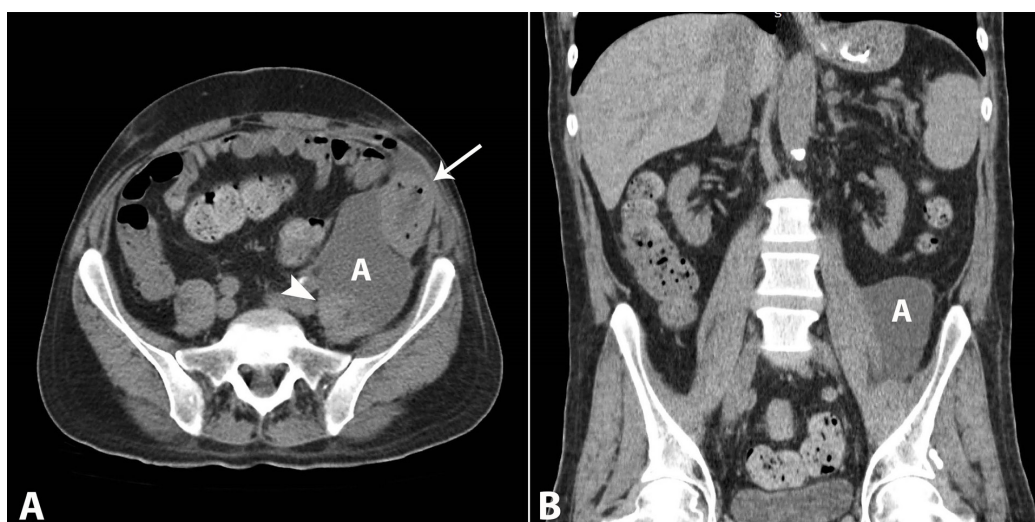
showed delayed graft function requiring hemodialysis for 15 days and, although the diuresis started on the 8th day after surgery, the serum creatinine values slowly decreased. The Doppler ultrasound was performed on the 1st day after the transplantation and no vascular complications were detected. During hospitalization, on the 10th day after the transplant, the patient was prescribed ertapenem for 13 days due to a urinary tract infection caused by ESBL+ *Klebsiella* sp. The immediate postoperative urine culture was negative. The patient also had phlebitis, and vancomycin was added to the treatment. On the 40th hospitalization day, an abdominal computed tomography (CT) showed the image consistent

with a lymphocele in the surgical site, involving the transplanted kidney, which was treated conservatively. At the end of the antibiotic therapy, the patient was discharged with steady creatinine levels of 5.5 mg/dL (reference value: 0.8–1.5mg/dL). At the time of hospital discharge, the urine culture was negative. After 45 days of the transplantation, even with adequate diuresis, serum creatinine values were still high. Therefore, a graft biopsy was performed, which showed a small area of ischemic necrosis, without evidence of signs of residual infection (Figure 1A and 1B). Arteries showed marked intimal fibrosis and a duplication of the internal elastic consistent with previous donor lesions. At surgery, arterial fibroelastosis was not observed



**Figure 1.** Photomicrography of the kidney biopsy 45 days after transplantation. **A** – Three areas of the sample are pointed out: (i) unspecific inflammatory process in the subcapsular area, indicated by a circle; (ii) coagulative necrosis, indicated by an arrow; and (iii) tubular degeneration and necrosis indicated by a square (H&E, 20x); **B** – Cortical with extensive tubular degeneration and necrosis. Note: there were no signs of rejection or infection (H&E, 100X); **C** – Extensive tubular hydropic degeneration with more detail (H&E, 400X); **D** – Medulla with intense edema and tubular necrosis; there was an absence of infectious inflammatory infiltrate and papillary necrosis (H&E, 100X).





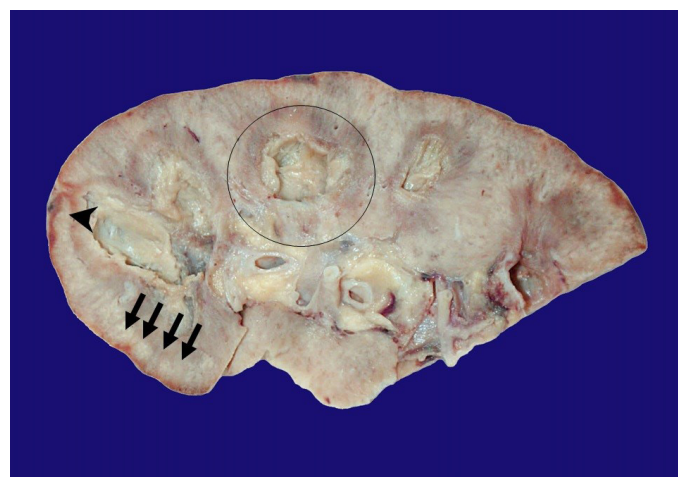
**Figure 2.** Abdominal CT images. **A** – Axial image: the graft surrounded by inflammatory process and gas (arrow) in contact with an abscess (A); perigraft abscess in close contact with the psoas muscle (arrowhead); **B** – Coronal plane. Note the abscess juxtaposed to the psoas muscle.

in the most superficial vessels of the implantation biopsy. There was no evidence of tubule-interstitial and vascular rejection. The immunofluorescence study revealed negativity for C4d. The urine culture was negative at this stage.

Two days after the biopsy, the patient returned to the emergency facility presenting severe sepsis due to urinary infection (*ESBL<sup>+</sup> Klebsiella sp.* was isolated from the urine and blood cultures) and was started on antibiotic therapy with imipenem. Over the following days, the patient progressed with worsening clinical status, presenting hypotension, tachycardia, and shock. The abdominal CT showed a homogeneous fluid collection, measuring  $9.4 \times 7.0$  cm, in the upper pole of the graft, with contiguity with the psoas muscle and a gaseous component in the pelvis and calices of the graft extending to subcutaneous tissue. These findings were consistent with EP and perigraft collection (Figure 2A and 2B).

Fluconazole and polymyxin B were added to the antibiotic regimen. On the same day, based on the clinical and radiological findings, surgical drainage of the collection and graft excision were undertaken. The intraoperative description reported a purulent collection in the upper pole of the graft. This material culture was positive for the same bacteria from the urine and blood cultures. After this procedure, the patient presented refractory septic shock and died.

The macroscopic examination of the surgical specimen showed a kidney measuring



**Figure 3.** Gross appearance of the longitudinal section of the formalin fixed transplanted kidney: cortical pale and swollen with multiple microabscesses (arrow) and tiny areas of subcapsular necrosis (arrowhead); medulla with necrotizing papillitis, indicated by a circle.

$10.0 \times 6.0 \times 4.0$  cm, weighing 95 grams, with an uneven surface, exhibiting pale areas of imprecise limits. The structures of the renal hilum were preserved. The kidney's cut surface showed diffuse pallor of the renal parenchyma with mild dilatation of the pelvis and ureter. The cortex was swollen and showed multiple small abscesses. Papillary necrosis was present, and most of the necrotic papilla sloughed into the lumen of the renal pelvis. There were also very small subcapsular areas of ischemic necrosis (Figure 3).

The histopathological study of the transplanted kidney was consistent with chronic suppurative

pyelonephritis with necrotizing papillitis. Histopathological findings showed an extensive acute inflammatory process with multiple abscesses in the cortical. Small areas of superficial ischemic necrosis were also seen. The medulla showed papillary necrosis characterized by ischemic necrosis surrounded by intensive suppurative inflammatory infiltration and calcium deposits. Newly formed vessels and fibrosis were observed in the renal parenchyma (Figure 4A, 4B, 4C, and 4D).

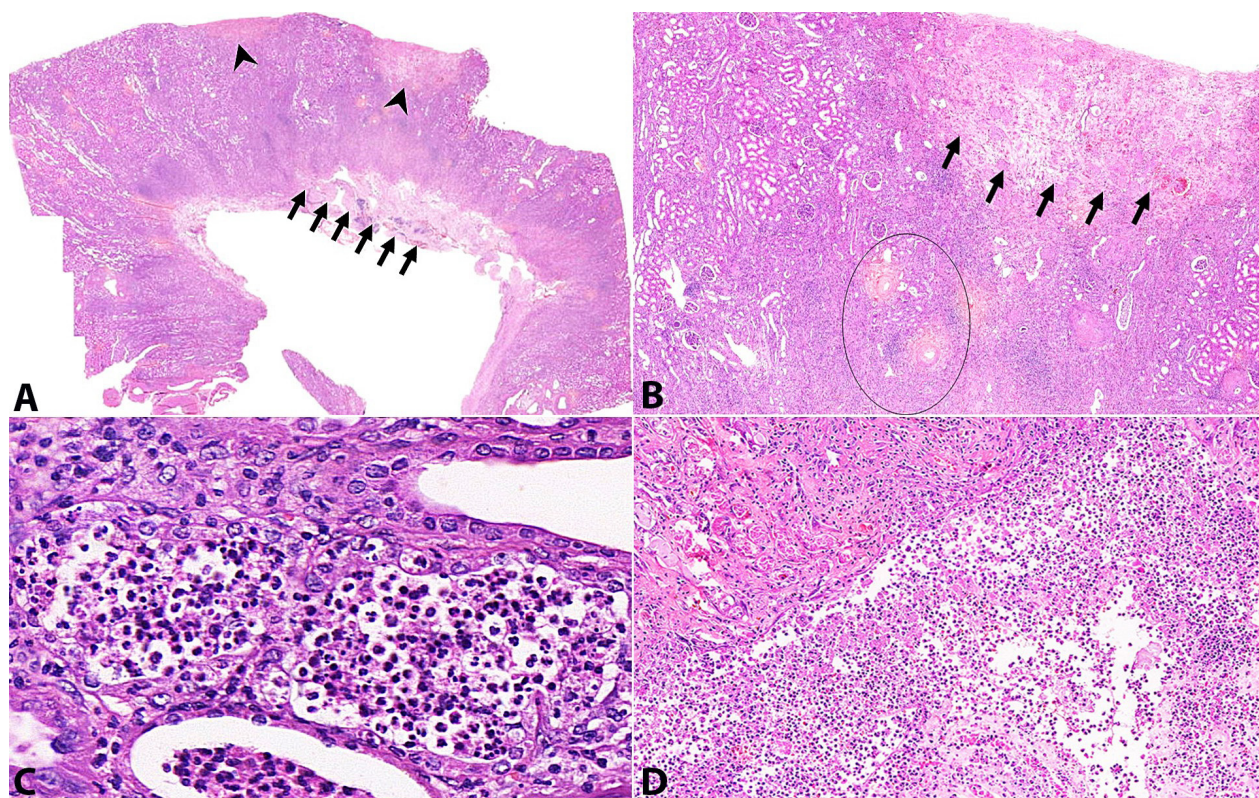
## DISCUSSION

EP is a rare disorder characterized by necrotizing kidney infection with the production of gas, which builds up in the parenchyma, the perirenal tissues and/or urinary collecting system. It is a pathological condition commonly diagnosed in patients with diabetes mellitus, with a mortality rate of up to 80% when improperly treated. After the 1970s, with the improvement of antibiotics and life support equipment

in the care of critically ill patients, mortality was reduced to the current rate of 20%.<sup>1</sup>

The most commonly involved etiological agents are represented by Gram-negative bacteria, especially *Escherichia coli*, identified in 43.6-69% of cases, followed by *Klebsiella* sp., *Proteus* sp., *Enterobacter* sp., and other agents, such as *Streptococcus* sp. and *Candida* sp.<sup>1,2</sup> In 2014, Arsene et al.<sup>3</sup> highlighted the combination of the presence of pathogenic fermenting bacteria in the presence of high levels of serum glucose and impaired tissue perfusion as being responsible for the fast development of this entity.<sup>3</sup>

Regarding the prognostic predictors, Lu et al.<sup>1</sup> conducted a retrospective study comprising 32 patients with EP, where hypoalbuminemia, bacteremia, hemodialysis, and shock were the initial presentation, which, added to polymicrobial infection, represented factors of a poor outcome. Indeed, shock and polymicrobial infection are the best markers that correlate with poor prognosis.<sup>1</sup> Our patient was readmitted presenting clinical signs of sepsis.



**Figure 4.** Photomicrography of the kidney. **A** – Chronic pyelonephritis with necrotizing papillitis (arrow) and, above this area, subcapsular coagulative necrosis (arrowhead) (H&E, 40X). **B** – Renal cortex with arterial fibroelastosis, indicated by a circle, at the bottom of a shallow area of coagulative necrosis (arrows) (H&E, 200X). **C** – Chronic pyelonephritis with abscesses (H&E, 400X). **D** – Necrotizing papillitis (H&E, 400X).



In 2012, Alexander et al.<sup>2</sup> reported a literature review comprising 22 cases of EP in transplant patients. These authors reviewed 20 of these 22 cases and showed that 18 patients had diabetes mellitus and aged between 12 and 76 years. In this series, the disease manifested within the period from 2 weeks to 15 years after the transplant. The main etiologic agent was *E. coli* (55%). Nine of the 20 reviewed patients underwent antibiotic therapy associated with graft excision, and seven received antibiotic therapy associated with percutaneous drainage. The remaining four patients received only antibiotics with full recovery after the treatment. Three deaths occurred among the group of patients who underwent the graft excision.<sup>2</sup>

Therapeutic schedules for EP are established according to the tomographic findings of the kidney and the perinephric tissues. The most widely used classification is that proposed by Huang and Tseng,<sup>5</sup> established by the tomographic evaluation of a native kidney. According to this classification, four classes are defined, which show a correlation with the mortality rate (Table 1). Classes 1, 2, and 3A allow antibiotic therapy and surgical drainage; however, the classes 3B and 4 require nephrectomy, especially when associated with other clinical data, such as hemodynamic instability and thrombocytopenia.<sup>2</sup>

The use of the Huang and Tseng classification<sup>5</sup> in the case of transplant patients was discussed by Al-Geizawi et al.<sup>4</sup> These authors emphasized that

transplant patients with EP, regardless the extension of the involvement, should be classified as Huang and Tseng Class 4, because, as renal grafts do not have Gerota's fascia, the spread of the infection to the surrounding tissues is easier.

In this context, Al-Geizawi et al.<sup>4</sup> studied 20 transplant patients who presented EP and, considering the renal function impairment (caused by the infection) as the single criterion, proposed a new classification (Table 2) with therapeutics purposes. Therefore, the treatment for Al-Geizawi's stage 1 classification should be antibiotics and close clinical surveillance with glycemic and electrolyte controls, as well as continuous assessment of immunosuppression. For stage 2, in addition to the latter precautions, surgical drainage and tomographic scans (to monitor the behavior of the infection's signs) should be added.<sup>4</sup> For stage 3, nephrectomy should be indicated in the case of transplanted kidneys.

Al-Geizawi et al.<sup>4</sup> reviewed the reports of 16 cases of EP in renal allografts described in the literature, and classified them according to their proposed classification. Among this group, 13 patients presented concordance between both classifications, which meant that the adopted therapeutics were the same regardless of the classification. However, in this study, among these 13 patients, two classified as Al-Geizawi's stage 3 died after nephrectomy, which was lately performed (five and four days after the

**Table 1.** Huang and Tseng<sup>5</sup> classification based on computed tomography findings, validated for patients with emphysematous pyelonephritis affecting the native kidney

Category	Definition	Risk of mortality
Class 1	Gas in the collecting system	Zero
Class 2	Gas in the renal parenchyma with no extension beyond the organ	10%
Class 3 A	Gas and/or abscess in perirenal space	29%
Class 3 B	Gas and/or abscess in para-renal space	19%
Class 4	Bilateral emphysematous pyelonephritis or affecting single solitary kidney	50%

**Table 2.** Classification of patients with emphysematous pyelonephritis, as Al-Geizawi et al<sup>4</sup>

Category	Definition	Risk of mortality
Stage 1	Gas in the collecting system	Zero
Stage 2	Gas least 50% of the renal parenchyma, with minimum extension to perirenal space, quickly controlled sepsis	Zero
Stage 3	Gas in more than 50% of the renal parenchyma or extensive spread to perirenal space or evidence of organ failure, or uncontrolled sepsis, or nonresponder shock to therapeutic measures	25%

diagnosis). Among the remaining patients, three presented discordance, namely: (i) one patient, classified as Al-Geizawi's stage 2, was treated with nephrectomy and presented a favorable outcome; (ii) one patient, classified as Al-Geizawi's stage 2, was treated with antibiotics without surgical drainage, also evolved favorably; and (iii) one patient, classified as Al-Geizawi's stage 3, was treated with antibiotics without nephrectomy presented a favorable outcome as well.<sup>4</sup>

There are few cases of EP in renal allografts, which limits a detailed evaluation of the Al-Geizawi classification. Despite the existence of these classifications, one should not be tied to them: the clinical status, if unsteady and deteriorating, should anticipate the decision by nephrectomy. Notwithstanding the concordance between the aforementioned classifications, two patients died because of the delay in surgical intervention. The success observed in two patients with Al-Geizawi's stages 2 and 3, respectively, who were treated exclusively with antibiotics, should not be seen as a rule. Delays in surgical interventions, either nephrectomy or drainage, may result in death.

CT evaluation is important for diagnosis, classification, and therapeutic scheduling in cases of EP. However, the clinical and laboratory evaluation, with attention to clinical features of sepsis and urine culture, must be taken as the priority mainly in patients at risk, such as patients with diabetes and those who are immunosuppressed, specifically with kidney transplants.<sup>6,7</sup> Alhajjaj and Pasha<sup>8</sup> reported a case similar to the case of our patient. These authors also stated the importance of a surgical approach in these cases due to the infection severity in the context of a patient with impaired immunity.

In the case presented herein, the first CT scan—after the first infection treatment—showed an image consistent with lymphocele, and the biopsy sampled small areas of necrosis, hemorrhage, and mild inflammatory process. After the second CT scan—during the second hospitalization—the patient underwent graft removal, which showed the pathologic findings similar to those reported by Archana et al.<sup>7</sup> in diabetic patients without kidney transplant: anemic infarctions, abscesses, and fibrosis.<sup>7</sup> Our patient had a progressively poor clinical outcome. In the context of the morphological aspects seen in the transplanted

kidney, it is likely that the patient had complicated pyelonephritis from the beginning, soon after the transplant. The first treatment did not eradicate the infection, although the culture was negative at the patient's hospital discharge. The infection relapse and the renal complications were also decisive for the poor outcome. The needle biopsy was important to rule out the possibility of rejection but failed to show the parenchymal infection. The small areas of superficial necrosis should be interpreted, in this case, as evidence of an infectious complication. Archana et al.<sup>7</sup> reported a case of EP in a diabetic patient showing microabscesses associated with areas of coagulative necrosis. They emphasized that EP is related to immunity and impaired tissue perfusion. In our case, the most impressive finding was the extensive and destructive infection in an immunosuppressed patient. The necrotic areas were superficial and very small. They should not be considered as infarctions. Thrombi were not found. The presence of arteriosclerosis and the microcirculation compression by the inflammatory process may have contributed to the development of the coagulative necrosis.

In our case, we disfavor the idea of vascular complication due to problems with the surgical anastomosis. The Doppler ultrasound on the first day after transplantation ruled out any vascular complications. The Doppler ultrasound on the first three days after transplantation was helpful to detect the acute graft dysfunctions as rejection and surgical complications.<sup>9</sup> This image data and the absence of thrombi in the surgical specimen disfavor any renal allograft thrombosis, a condition responsible for 2-7% of early allograft losses in adults occurring in the postoperative period, with a peak incidence of 48 hours. Thrombosis may be related to technical problems during the vascular clamp or, in some cases, to the presence of atheroma, which represents the only independent factor associated with the risk of arterial renal thrombosis.<sup>10</sup>

Despite the existence of EP classification, the utility of the CT, and the urine culture for therapeutic scheduling, the signs of disease severity should always be placed first and considered for more accurate treatment decisions. In fact, biopsies are not needed for this diagnosis. However, their importance relies on clarifying the differential diagnosis and, maybe, in

revealing the signs of morphological complications, as seen in this case.

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