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von Brünn Nests Hyperplasia as a Cause of Ureteral Stenosis After Kidney Transplantation

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INTRODUCTION

Urologic complications occur in 2.5% to 20% of patients after kidney transplantation, and are an important cause of allograft loss and patient morbidity.[1–6] The most frequent technical adverse events stem from complications of the ureterovesical anastomosis, including urinary fistulae, and stenosis.[3] An intrinsic ureteral stricture can also occur as a consequence of local inflammation, infection, or inadequate vascularization resulting in ischemia of the ureteral transplant.[1,6]

Von Brünn nests are considered as a variant of the normal urinary tract histology, and originate from the proliferation of benign urothelial cells within the lamina propria.[7–9] This particular structure develops mainly in the bladder, but can also be found in the ureters. To date, von Brünn nests have not been described as a potential cause of ureteral stenosis.

Here, we report the first known case of post-transplantation obstructive kidney failure due to the hyperplasia of ureteral von Brünn nests, analyze the origin of the proliferating cells, and discuss pathophysiological mechanisms and potential clinical implications.

CASE PRESENTATION

A 63-year-old man with end-stage kidney disease due to IgA nephropathy received a kidney transplant from a deceased donor. Computed tomography performed in the 60-year-old female donor had revealed no specific anomaly of the kidneys or of the urinary tract. During the preparation of the allograft, the macroscopic appearances of the kidney and the ureter were unremarkable. The kidney was implanted in the left iliac fossa. A double J stent was used for the ureteric reimplantation, and no significant issue was noted during the surgical procedure. The cold and warm ischemia times were 8 hours and 65 minutes, respectively. The standardized immunosuppressive regimen prescribed to the patient included basiliximab and methylprednisolone pulses as the induction treatment, followed by tacrolimus, mycophenolate mofetil, and prednisolone. The postoperative outcome was favorable. No infection was recorded. Plasma creatinine was 1.3 mg/dl 14 days after transplantation and remained stable until the double J stent was removed 4 weeks later, in accordance with the local protocol.

Three months after the removal of the double J stent, the patient's plasma creatinine increased from 1.3 to 1.8 mg/dl within 3 weeks. A urinary tract ultrasound was performed, and showed a large, 28-mm dilatation of the allograft pelvis. This dilatation was confirmed by a computed tomography scan (Figure 1). The radiological appearance suggested that the stenosis was located mainly in the very proximal part of the ureter below the pelviureteral junction, mimicking a pyeloureteral junction syndrome. A furosemide ^{99m}Tc-MAG3 scintigraphy revealed slow clearance of pelvicalyceal and ureteral activity in the allograft, consistent with a pathophysiological significance of the obstruction. The decision was taken to perform a pyeloureteral anastomosis with the left native ureter, and to resect the donor ureter for histological analysis. The patient initially refused the urological management, and neither temporary stent placement nor retrograde ureteropyelography was performed in this context. The follow-up showed persistent hydronephrosis. Plasma creatinine progressively increased,

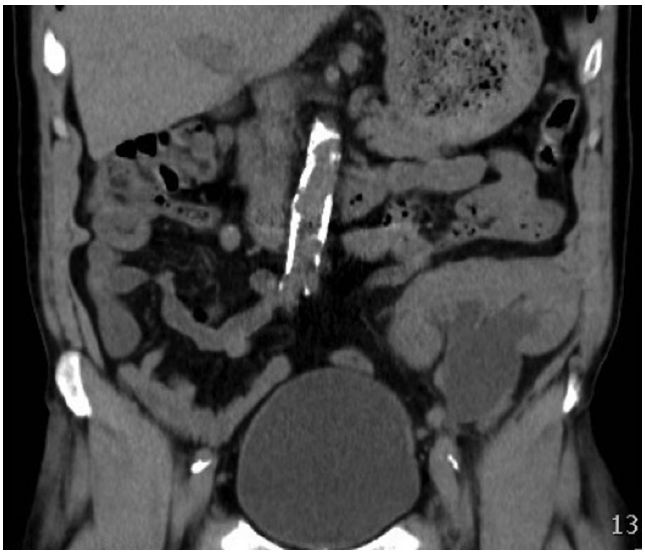

Figure 1. Computed tomography scanner. Pyelocalyceal dilatation and dilatation of the proximal ureter.

up to 2.3 mg/dl when the pyeloureteral anastomosis was finally performed 3 months after the diagnosis.

After surgery, plasma creatinine decreased to 1.4 mg/dl. Pathological analysis of the ureteral allograft (pyeloureteral junction and a 3-cm-long fragment of the proximal ureter) revealed a multifocal narrowing of the lumen due to a florid circumferential hyperplasia of von Brünn nests strictly limited to the lamina propria, within the ureteral wall (Figure 2 and Supplementary Figure S1).

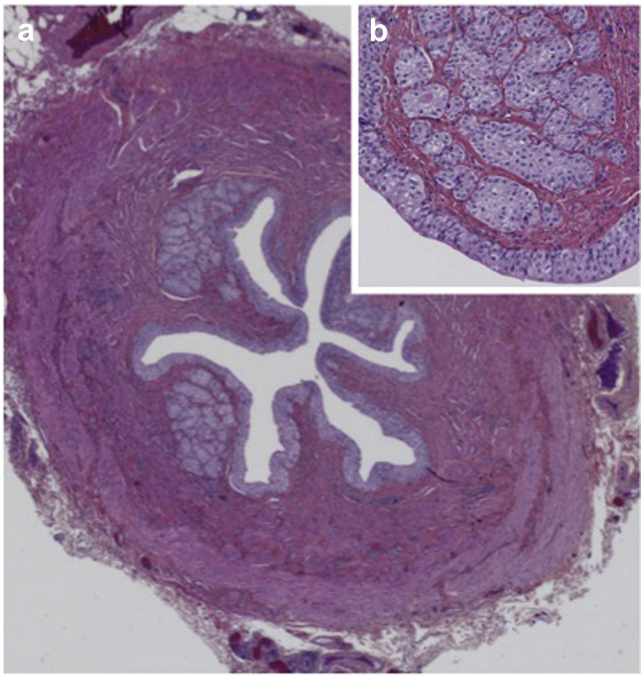

Figure 2. Histological analysis of the proximal part of the allograft ureter. Hyperplasia of von Brünn nests, characterized by multifocal proliferation in the lamina propria, devoid of cellular atypia. Hematoxylin and eosin safran staining. Original magnification (a) ×10, (b) ×40.

No atypia was present, and SV40 staining was negative. To determine whether the von Brünn nests stemmed from the donor or whether they were a retrograde proliferation originating from the recipient's bladder, we took advantage of the sex difference between the 2 subjects. We performed a fluorescence *in situ* hybridization (FISH) with CEP "X" and "Y" probes (DXZ1 and DYZ3, Vysis kit, Abbott, Rungis, France) on both the allograft ureter and on a biopsy of the proximal left native ureter. External controls were satisfactory. The internal control (native ureter) presented a characteristic "XY" phenotype, as expected. We found a double "XX" fluorescence within the von Brünn nests, confirming the donor origin (Figure 3). Over an 18-month follow-up, plasma creatinine was stable, and no recurrence or additional urological complication was noted.

DISCUSSION

Von Brünn nests are benign proliferative and metaplastic lesions of the urinary tract. They are caused by the invagination of overlying urothelial cells, which aggregate into round nests within the superficial lamina propria.[7,9,10] Their most frequent location is the bladder trigone and the submucosa of the pelviureteral junction. This specific histological condition can be highly prevalent, with autopsy series revealing that up to 90% of bladders present with von Brünn nests.[9] Von Brünn nests are usually devoid of atypia; however, they can undergo hyperplasia and become visible on bladder cystoscopy as pink or white submucosal blebs. More rarely, they can undergo central cystic degeneration (cystitis cystica), or atypical glandular differenciation (cystitis glandularis) and become visible on ultrasound.[7,11,12] The main differential diagnosis is nested cell urothelial carcinoma.[12–14] This diagnosis can be excluded in our patient because of the focal localization limited to the lamina propria, the absence of cellular atypia, and the favorable evolution. In rare cases, von Brünn nests can lead to obstruction of the cystic outlet or of the ureterovesical junction, after cystic degeneration.[8,10,11]

To the best of our knowledge, hyperplasia of von Brünn nests has not been described as a potential cause of ureteral stenosis below the pelviureteral junction, and no urological complication related to von Brünn nests in solid organ transplant recipients has been previously reported. In our case, after careful reviewing of the clinical, laboratory, radiologic, peroperative, and pathological data, no argument for an alternative ischemic, infectious, neoplastic, or mechanical cause of this incomplete ureteral stenosis was found. Because of the artifactual increase in the lumen diameter due to fixation, the photograph shown in

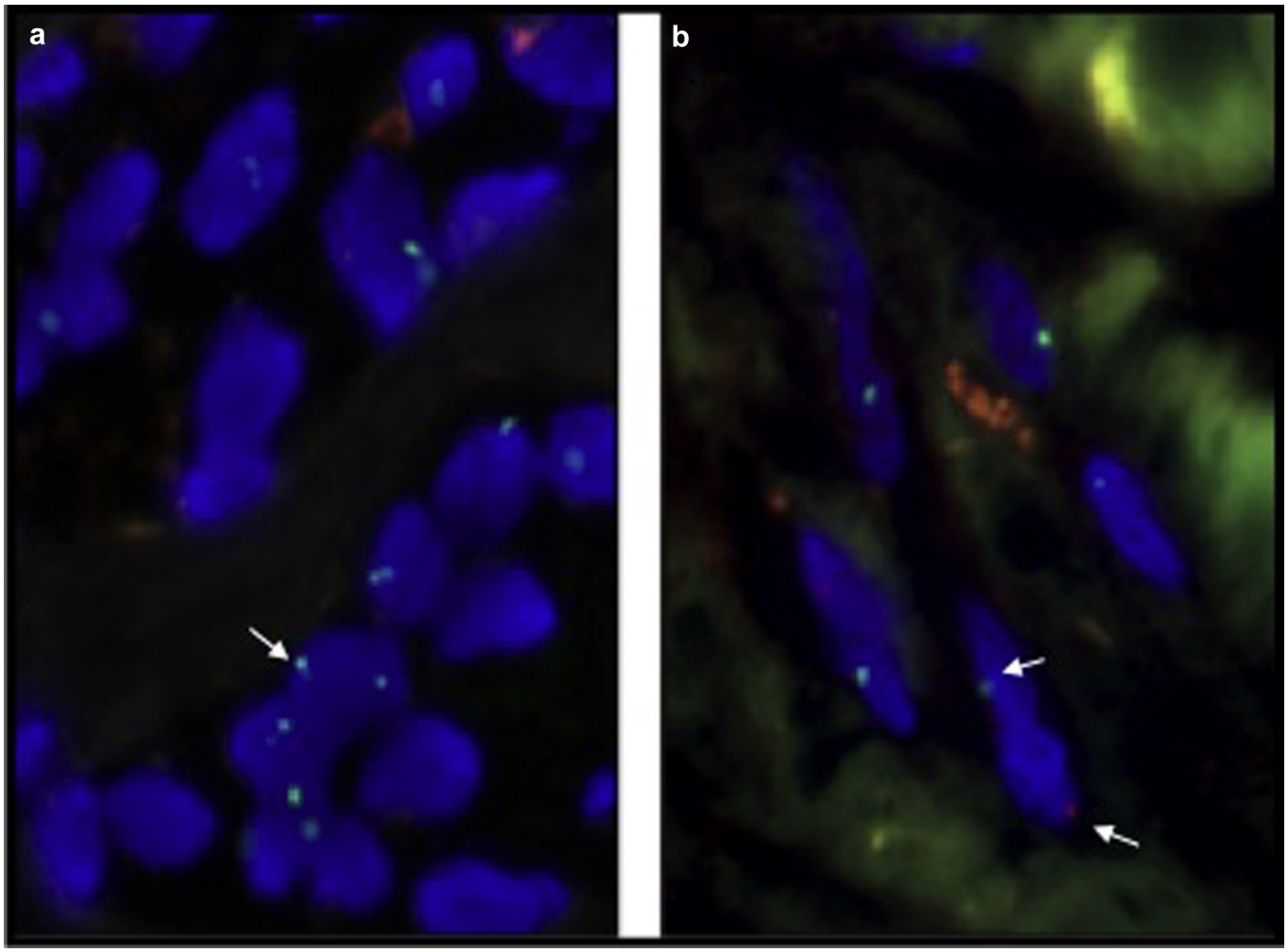

Figure 3. Fluorescence *in situ* hybridization of (a) the allograft and (b) the native ureters. The X chromosome is revealed by the green probe and the Y chromosome by the red probe. (a) Von Brünn nests exclusively present X probes (arrow) in the allograft ureter, which demonstrates that the proliferation originates from the donor. (b) As expected, in the recipient's native ureter, X and Y probes (arrows) were expressed together.

Figure 2 most likely underestimates the narrowing of the ureteral lumen present *in vivo*. In addition, the blood flow, edema, and contraction of the ureteral smooth muscle cells are dynamic factors that further decrease the diameter of the lumen, whereas they are totally absent when evaluated on pathological material.

In kidney transplant recipients, proliferative lesions of the urinary tract can originate from local or metaplastic growth of recipient cells or of donor-transmitted cells, as is the case in nephrogenic adenoma.[15] Here, using fluorescence *in situ* hybridization, we demonstrated that the ureteral obstruction was the direct consequence of local hyperplasia of donor-transmitted cells. Importantly, the donor's initial CT scan was unremarkable, and the contralateral kidney presented with no pyelocalyceal dilatation 6 months after transplantation in the other recipient, which suggests that specific factors in our patient triggered post-transplantation hyperplasia of the preexisting von Brünn nests.

Pathophysiological mechanisms leading to hyperplasia of von Brünn nests have been poorly studied, but are believed to include ischemia, infection, inflammation, chemotherapy, and radiotherapy.[7,9–11,16,17] One study has shown that cells of von Brünn nests synthesize and express fibroblast growth factor (FGF)−10 receptor, and that a paracrine synthesis of FGF-10 is present in the vicinity of von Brünn nests in the exstrophic bladder.[18] FGF-related signaling could therefore be a key factor in the proliferation of von Brünn nests.[19] Vinsonneau *et al*. have demonstrated that urothelial proliferation happens following ischemic injury, and, interestingly, that this event is dependent on fibroblast growth factor signaling.[20] In this context, we speculate that the transplantation-related ischemia contributed to the hyperplasia of the preexisting von Brünn nests in our patient. In addition, although no infection was recorded during the posttransplantation period, the insertion of the double J stent and its presence during 4 weeks may have induced and sustained local inflammation.

No specific management has been suggested for von Brünn nest hyperplasia, except for the treatment of potential inducing factors. This is most likely because of the benign nature of the proliferation and the rarity of complications. In our case, the diagnosis was not suspected before the results of the histological analysis. Whether the proliferation and the chronic obstruction could have been improved with an alternative medical management, for example with high-dose corticosteroids, is uncertain.[16] No spontaneous improvement was observed, although the patient decided to postpone the surgery. Ultimately, the pyeloureteral anastomosis offered a definitive treatment.

In conclusion, this case presents an unusual and potentially underestimated cause of obstructive decrease in kidney function after transplantation. Awareness of this condition can be useful for nephrologists, urologists, radiologists, and pathologists involved in the care of solid organ transplant recipients.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Figure S1. Histological analysis of the proximal allograft ureter, a few cm distal to that shown in Figure 2. Hematoxylin and eosin safran staining. Original magnification (A) ×10, (B) ×40.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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