Retroperitoneal fibrosis in feline renal transplant recipients: 29 cases (1998–2011)

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Objective—To evaluate features, treatment, and prognosis associated with retroperitoneal fibrosis that developed after renal transplantation in cats.

Design—Retrospective case series.

Animals—29 cats.

Procedures—Medical records of cats that developed retroperitoneal fibrosis after renal transplantation at the College of Veterinary Medicine, University of Pennsylvania, between 1998 and 2011 were reviewed for signalment, date of transplantation, age, results of urine and blood analyses, blood pressure at the time of diagnosis, infectious disease and medication anamneses, anesthetic protocols, and intraoperative complications.

Results—Of 138 transplant recipients, 29 (21%) developed clinically important retroperitoneal fibrosis. Nineteen (66%) were male, and median age at the time of renal transplantation was 8 years (range, 4 to 13 years). Median number of days after transplantation to diagnosis of retroperitoneal fibrosis was 62 (range, 4 to 730 days; mean, 125 days). The most common clinical signs were lethargy and anorexia. All affected cats were azotemic (BUN concentration > 32 mg/dL; creatinine concentration > 2.0 mg/dL) and anemic (PCV < 29%) at the time of retroperitoneal fibrosis diagnosis, although cats were nonazotemic at the time of discharge following transplantation, and anemia was less pronounced. Twenty-five cats successfully underwent surgical ureterolysis in which scar tissue was dissected away from the allograft ureter to relieve extraluminal compression. Retroperitoneal fibrosis recurred in 6 (22%) cats a median of 180 days (range, 8 to 343 days) following the original diagnosis and was treated successfully by repeated ureterolysis.

Conclusions and Clinical Relevance—Retroperitoneal fibrosis occurred in a substantial percentage of feline renal transplant recipients and should be considered a differential diagnosis in any feline renal transplant recipient with clinicopathologic findings, imaging abnormalities, or signs suggestive of obstructive uropathy. (J Am Vet Med Assoc 2013;243:1580–1585)
Results

During the study period, 138 cats underwent renal transplantation at the University of Pennsylvania. Of the cats that underwent renal transplantation, 29 developed clinically important retroperitoneal fibrosis and were included in the study. Of these, 10 were spayed females and 19 were neutered males. The majority (23/29 [79%]) were domestic shorthairs, although other breeds included domestic longhair (2), Abyssinian (2), and Siamese (2). Median age at the time of renal transplantation was 8 years (range, 4 to 13 years). All cats included in the study were administered appropriate immunosuppressive treatments prior to surgery, including the calcineurin inhibitor cyclosporine (1 to 4 mg/kg [0.45 to 1.82 mg/lb], PO, q 12 h) in conjunction with the corticosteroid prednisolone (0.5 to 1 mg/kg [0.23 to 0.45 mg/lb], PO, q 12 to 24 h). None of the cats had positive results of bacteriologic culture of urine at the time of renal transplantation; however, 8 cats had a history of urinary tract infection. Four cats had a history of calcium oxalate urolithiasis. Three cats were seropositive (lgG) for Toxoplasma gondii at the time of evaluation for renal transplantation. These cats were administered clindamycin (10 mg/kg [4.5 mg/lb], PO, q 12 h) prophylactically at the time immunosuppression was initiated, and lifelong administration was recommended. Three cats had a history of recurrent rhinitis consistent with infection of the upper portion of the respiratory tract with herpesvirus and had been administered L-lysine treatment (250 mg, q 12 h). One cat had skin lesions consistent with dermatophytosis; this was confirmed by fungal culture, and the cat was administered systemic antifungal treatment (itraconazole; 5 mg/kg [2.3 mg/lb], PO, q 24 h) prior to immunosuppression.

At the time of renal transplantation, all cats included in the study were administered cefazolin (22 mg/kg [10 mg/lb], IV, administered at induction and then every 90 minutes during surgery). Antimicrobial regimens used during the postoperative period included treatment with cefazolin (22 mg/kg, IV, q 8 h, for 1 to 3 days after surgery; n = 18 cats), enrofloxacin (5 mg/kg, IV or PO, q 24 h, for 5 to 10 days after surgery; 15 cats), amoxicillin clavulanate (12 to 18 mg/kg [5.5 to 8.2 mg/lb], PO, q 12 h, for 5 to 14 days after surgery; 12 cats), ampicillin (15 to 22 mg/kg [6.8 to 10.0 mg/lb], IV, q 8 h, for 2 to 4 days after surgery; 3 cats), cefpodoxime (5 to 7 mg/kg [2.3 to 3.2 mg/lb], PO, q 24 h, for 5 to 7 days after surgery; 2 cats), imipenem (5 mg/kg, IV, q 8 h, for 2 days after surgery; 1 cat), metronidazole (7.5 mg/kg [3.4 mg/lb], PO, q 12 h, for 5 days after surgery; 1 cat), doxycycline (5 mg/kg, PO, q 12 h, for 7 days after surgery; 1 cat), erythromycin (15 mg/kg, PO, q 12 h, for 10 days after surgery; 1 cat), azithromycin (10 mg/kg, PO, q 24 h, for 10 days after surgery; 1 cat), ticarcillin clavulanate (50 mg/kg [22.7 mg/lb], IV, q 6 h for 2 days after surgery; 1 cat), and amoxicillin (22 mg/kg, PO, q 12 h, for 7 days after surgery; 1 cat). Antimicrobial regimens were chosen on the basis of clinician preference or the cats infectious disease history. Two cats received atenolol (6.25 mg, PO, q 24 h), and 2 cats received amiodopine (0.0625 mg, PO, q 24 h) for management of postoperative hypertension.

The median number of days after transplantation to the time of retroperitoneal fibrosis diagnosis was 62 days (range, 4 to 730 days; mean, 125 days). The most common clinical signs upon reevaluation because of retroperitoneal fibrosis were lethargy (11 cats) and anorexia (12 cats). Other signs included vomiting (3 cats), decreased urination (1 cat), polyuria and polydipsia (1 cat), constipation (2 cats), and seizures (1 cat). Fourteen cats were subclinically affected but abnormalities were detected on routine follow-up laboratory evaluation.

At the time of retroperitoneal fibrosis diagnosis, all cats were azotemic (BUN concentration > 32 mg/dl; creatinine concentration > 2.0 mg/dl); median BUN and creatinine concentrations were 84 mg/dl (range, 42 to 206 mg/dl) and 4.0 mg/dl (range, 2.2 to 11.7 mg/dl), respectively. These cats were nonazotemic at postoperative discharge following renal transplantation. All cats were anemic (median PCV, 24%; range, 15% to 32%; reference range, 35% to 50%). In comparison, the median PCV at postoperative discharge following renal transplantation was 30% (range, 24% to 37%). Median urine specific gravity was 1.010 (range, 1.006 to 1.024) at the time of retroperitoneal fibrosis diagnosis and 1.031 (range, 1.023 to 1.041) following renal transplantation. Median systolic arterial blood pressure of the cats was 150 mm Hg (range, 108 to 180 mm Hg; reference range, 100 to 150 mm Hg), which was similar...
to the median blood pressures of the cats after surgery (median, 144 mm Hg; range, 100 to 172 mm Hg). However, 3 cats that were normotensive after renal transplantation were persistently hypertensive (systolic arterial blood pressure > 170 mm Hg) when reevaluated for retroperitoneal fibrosis.

Two cats had microbial growth on bacteriologic culture of urine; these cats had a history of urinary tract infection but negative results of bacteriologic culture of urine at the time of renal transplantation. Of the 4 cats with a history of calcium oxalate urolithiasis, all developed retroperitoneal fibrosis. Following the diagnosis of retroperitoneal fibrosis, repeated infectious disease testing was performed in affected cats. Two cats that were seronegative for toxoplasmosis at the time of renal transplantation screening were seropositive (IgG) at the time of fibrosis diagnosis and were then administered clindamycin (10 mg/kg, PO, q 12 h). One cat had bartonellosis, which was diagnosed by use of western blot analysis, and 3 cats had Campylobacter enterocolitis, which was diagnosed by use of bacteriologic culture of feces; these cats were treated with azithromycin (10 mg/kg, PO, q 24 h) and erythromycin (15 mg/kg, PO, q 12 h), respectively. One cat had feline infectious peritonitis, which was diagnosed at the time of necropsy following euthanasia 2 years following retroperitoneal fibrosis diagnosis. Five of 29 cats had diabetes mellitus, which was diagnosed following renal transplantation on the basis of persistent hyperglycemia, glucosuria, and clinical signs including polyuria, polydipsia, and polyphagia. The diagnosis of diabetes mellitus was made prior to retroperitoneal fibrosis diagnosis in 2 cats (4 months and 1 year) and following the diagnosis in 3 cats (6 months, 1 year, and 3.5 years).

In the majority of cats (25/29 [86%]), a tentative diagnosis of retroperitoneal fibrosis was made on the basis of abnormalities detected with abdominal ultrasonography, in particular pyelectasia and hydronephrosis of the allograft kidney (25 cats), absence of obstructive urolithiasis (25 cats), and an inability to identify the allograft ureter suggestive of ureteral obstruction secondary to retroperitoneal scar tissue formation (23 cats). Computed tomography was used in conjunction with abdominal ultrasonography in 2 cats to look for evidence of extraluminal ureteral obstruction. Three cats were euthanized because of recurrent azotemia, and retroperitoneal fibrosis was confirmed at necropsy. In 1 cat, retroperitoneal fibrosis was identified at necropsy following euthanasia for unrelated disease (heart failure) 3 years following renal transplantation.

Twenty-five cats underwent exploratory surgery. Anesthetic induction and maintenance protocols were determined at the discretion of attending clinicians and varied among cats. At the time of abdominal exploratory surgery, ureterolysis was performed in all cats until the ureter was adequately released from constrictive fibrotic tissue. In 12 cases, cystotomy was also performed to confirm the reestablishment of appropriate urine flow through the allograft ureter. Macroscopically, the fibrosis was characterized as a dense, white tissue surrounding various parts of the allograft kidney and ureter (Figures 1 and 2). Histologic analysis on resected retroperitoneal tissue was performed in 10 cats and revealed a combination of smooth muscle, fibrous connective tissue, and mixed inflammatory infiltrate. Tissue samples were submitted for bacteriologic culture and antimicrobial susceptibility testing in 6 cats, and no microbial growth was identified in any of the samples. Surgical complications at the time of ureterolysis were reported in only 1 cat (postoperative uroabdomen). Six cats developed a known recurrence of the disease 8 to 343 days following the original retroperitoneal fibrosis and were treated successfully by repeated ureterolysis.

**Discussion**

Results of this study suggested that cats that undergo renal transplantation may have a high risk of developing retroperitoneal fibrosis, considering that 29 of 138 (21%) cats that underwent transplant surgery at the University of Pennsylvania developed this complication. To the authors’ knowledge, this complication has not been reported by other veterinary institutions. Whether the disparity is related to the surgical techniques used, patient population, or medical treatments...
is uncertain. It should be mentioned that the true prevalence of this condition in the feline renal transplantation population is unknown, given that only patients that developed clinically important disease, including nonspecific signs such as lethargy and anorexia, recurrence of azotemia, and abnormalities detected on abdominal ultrasonography (pyelectasia or hydronephrosis), were identified.

Three cats that were normotensive at the time of transplantation were hypertensive (systolic arterial blood pressure > 170 mm Hg) at the time of retroperitoneal fibrosis diagnosis. Hypertension is commonly associated with hydronephrosis caused by ureteral obstruction and is thought to be secondary to decreased renal perfusion with subsequent activation of the renin-angiotensin cascade. Thus, serial blood pressure monitoring at recheck examinations may prove beneficial when monitoring for early signs of obstructive uropathy.

In this study, ultrasonography was used as the sole imaging modality in most cats because the findings were sufficient to warrant abdominal exploration in most cases. However, it should be noted that more advanced imaging techniques are commonly used in human medicine, including IV urography, CT, and MRI. Computed tomography and MRI are considered the most sensitive imaging modalities for the diagnosis of retroperitoneal fibrosis and can sometimes help distinguish between primary and secondary disease processes.

The precise risk factors for retroperitoneal fibrosis have not been identified in cats, and the etiology is most likely multifactorial. In humans, most cases of retroperitoneal fibrosis are considered idiopathic. However, the disease has also been associated with the use of certain drugs, in particular ergot alkaloids (methysergide and ergotamine) used for migraine headache, dopamine agonists used for treatment of parkinsonism ( pergolide and methyldopa), antihypertensives (hydralazine and β-receptor antagonists), antimicrobials (ampicillin), and certain analgesics (aspirin and phenacetin). All cats in the present study were administered antimicrobials after renal transplantation, and 2 cats were administered a β-receptor antagonist (atenolol); however, it is unclear whether administration of these drugs played a role in the development of fibrosis. Cases of retroperitoneal fibrosis occurring secondary to malignant neoplasia, including Hodgkin’s and non-Hodgkin’s lymphoma, sarcomas, and carcinomas of the colon, prostate, breast, and stomach, have also been reported in the human medical literature. It is thought that in the case of malignant disease, fibrosis results from a primary tumor in the retroperitoneal space causing secondary inflammatory changes or a desmoplastic response to retroperitoneal metastasis. None of the cats in the present study had cancer at the time of diagnosis. However, 1 cat developed gastrointestinal lymphosarcoma 3 years after the diagnosis, and another cat developed hepatic carcinoma 9 months after the diagnosis.

Infectious diseases (tuberculosis, histoplasmosis, and actinomycosis) have been associated with retroperitoneal fibrosis in humans, usually by local spread of the disease into the retroperitoneal space resulting in exuberant inflammation. At our institution, all renal transplantation candidates are thoroughly screened for infectious diseases prior to surgery. However, 7 of the cats included in this study had infectious diseases at the time of renal transplantation, including toxoplasmosis ( n = 3), herpesvirus infection (3), and dermatophytosis (1). Following transplantation, an additional 2 cats developed toxoplasmosis, 1 cat developed bartonellosis, 3 cats developed Campylobacter enterocolitis, and 1 cat developed coronavirus infection (feline infectious peritonitis). Thus, the rate of posttransplantation infectious disease in this population of cats was high (14/29 [48%]). Although results of bacteriologic cultures of retroperitoneal tissue performed in 6 of the cats at the time of ureterolysis were negative for bacterial and fungal growth, infectious disease testing on resected scar tissue was not performed in all cases. In addition, tissues were not tested by PCR analysis for toxoplasma DNA, which would have been particularly pertinent in the 3 cats that seroconverted between the time of transplantation and the time of fibrosis diagnosis. Therefore, an infectious disease etiology cannot be ruled out in this study.

Five of 29 affected cats had diabetes mellitus after transplantation. A previous study revealed a rate of diabetes mellitus in cats that had renal transplantation 2.5 times that in cats with chronic renal failure and no transplantation. Presently, it is unknown whether the frequency of posttransplantation hyperglycemia is higher in cats that develop retroperitoneal fibrosis, compared with cats that do not develop retroperitoneal fibrosis, or whether hyperglycemia may be a contributing factor to scar tissue formation. In the human literature, a correlation between diabetes mellitus and fibrotic diseases has been identified; the end products of glucose metabolism play an important role in the development of fibrotic changes in multiple organs, including the lungs, kidneys, and arteries. Similar correlations have not been reported in the veterinary literature.

The mainstay of treatment for humans with idiopathic retroperitoneal fibrosis is administration of corticosteroids, which have anti-inflammatory effects, suppress cytokine production, inhibit collagen synthesis and maturation, and often lead to improvement in clinical signs, regression of retroperitoneal fibrotic tissue, and resolution of ureteral obstruction. If necessary, multiagent protocols can be used. All cats in the present study were consistently administered immunosuppressives after renal transplantation to prevent allograft rejection, and retroperitoneal fibrosis occurred despite treatment. Most humans with retroperitoneal fibrosis are not receiving immunosuppressives at the time of diagnosis.

In the present study, 25 cats were treated surgically to resect the fibrotic tissue that was causing ureteral obstruction. In human patients, surgery is only used in cases refractory to medical management and involves exploratory laparotomy for retroperitoneal biopsy, ureterolysis, and omentalization. Laparoscopic ureterolysis has also been described as well as the placement of temporary ureteral stents or nephrostomy tubes in cases of severe ureteral obstruction. In human patients, recurrence of disease is estimated at approxi-
mately 50% in patients that undergo surgery alone and only 10% in patients treated with corticosteroids with or without surgical intervention. Recurrence of clinically important fibrosis in the cats reported here was approximately 22%. This study was limited in that a control group (cats that had renal transplantation and did not develop retroperitoneal fibrosis) for comparison was lacking, mainly because follow-up abdominal imaging was not performed unless clinically indicated. This could be addressed in future studies by having ultrasonographic studies performed on all transplant patients at routine postoperative intervals, although such additional monitoring may be cost prohibitive or cause stress to patients. Retroperitoneal fibrosis in humans has been associated with aortic atherosclerosis. Although atherosclerotic disease is uncommon in cats, it would be prudent to historically examine aortic tissue that is removed at the time of aortotomy during feline renal transplantation. Collection of blood samples at the time of renal transplantation and the time of retroperitoneal fibrosis diagnosis to test for markers of systemic inflammation (acute-phase proteins and cytokines) might yield valuable information. A study of the use of multiagent immunosuppressive treatment and retroperitoneal fibrosis formation may provide insight into appropriate medical management for prevention or treatment of this disease in the future. Lastly, it should be noted that although the authors compared retroperitoneal fibrosis in feline transplant recipients to what seems to be a similar disease process in humans, the condition is not the same disease due to the fact that although the authors compared retroperitoneal fibrosis (“periaortitis”), variants, variations, patterns and pitfalls. The spectrum of disease in the future. Lastly, it should be noted that although the authors compared retroperitoneal fibrosis in feline transplant recipients to what seems to be a similar disease process in humans, the condition is still poorly elucidated in both species, and these comparisons should be interpreted cautiously.

References

44. Recurrence of clini-


From this month’s AJVR

Short-term effect of ovariectomy on measures of insulin sensitivity and response to dexamethasone administration in horses

François R. Bertin et al

Objective—To evaluate the effect of ovariectomy on insulin sensitivity in horses and determine whether the effects of suppression of the hypothalmo-pituitary-adrenal axis differ before and after ovariectomy.

Animals—6 healthy mares.

Procedures—The horses underwent an IV glucose tolerance test (IVGTT), an insulin sensitivity test, and a dexamethasone suppression test before and 5 weeks after ovariectomy. Body weight, serum cortisol and plasma ACTH concentrations, serum insulin-to-blood glucose concentration ratios, and changes in blood glucose concentration with time after injection of glucose or insulin were compared before and after ovariectomy.

Results—The dexamethasone injection resulted in a decrease in serum cortisol concentration before and after ovariectomy. In all horses, baseline plasma ACTH concentrations were within the reference range before and after ovariectomy. For each mare, results of an IVGTT before and after ovariectomy were considered normal. No significant differences in basal blood glucose concentration or time to reach baseline glucose concentration after an IVGTT were observed. Basal serum insulin concentration and serum insulin-to-blood glucose concentration ratios were not significantly different before or after ovariectomy, nor was the mean time to attain a 50% decrease in blood glucose concentration after insulin injection.

Conclusions and Clinical Relevance—Results indicated that ovariectomy does not appear to modify dexamethasone response in horses and that it does not modify short-term measures of insulin sensitivity. Findings suggested that horses undergoing ovariectomy are not at higher risk of developing equine metabolic syndrome or hypothalmo-pituitary-adrenal axis dysfunction and associated morbidity. (Am J Vet Res 2013;74:1506–1513)