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Original Research Article

A Review Article on Genitourinary Malakoplakia after Kidney Transplantation

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Abstract

Malakoplakia has been rarely reported in renal transplant recipients. We discuss two renal transplant recipients with malakoplakia involving renal allografts. Both transplant recipients were managed with reducing the doses of immunosuppressive medications and long-term oral antibiotic therapy. The renal allograft functions remained stable and imaging studies did not show progression of the disease. Our data suggest reducing the immunosuppression and long-term antimicrobial therapy to achieve long-term renal allograft survival.

Keywords: Transplantation, Urinary tract infections, Infectious diseases, Drugs.

INTRODUCTION

Malakoplakia is a chronic inflammatory condition associated with gram negative bacterial infections [1]. It also appears to be associated with immunosuppressive therapy after organ transplantation although it can also occur in immunocompetent patients [1-2]. Morphologically, it is similar to a pseudotumor and commonly involves the urinary bladder and kidneys [1-4]. It is histologically characterized by Michaelis-Gutmann bodies [1-5]. Here, we present the outcome of two patients with malakoplakia following kidney transplantation. We also reviewed the literature on the management of malakoplakia after kidney transplantation.

Case 1

A 74-year old female received a deceased renal transplant in 2012. The underlying renal disease remained unclear before transplantation. She did not receive any immunosuppressive medication prior to transplantation. She received induction therapy at the time of transplantation with rabbit-antithymocyte globulin. Following operation, she maintained on immunosuppression therapy including tacrolimus (achieving trough levels 6-7 ng/ml in first year then 5 ng/ml after that), mycophenolic sodium and prednisone (titrating down to 15mg every other day). She did not develop allograft rejection after transplantation. Her post-transplant baseline serum creatinine was 70 µmol/L. She developed multiple episodes of urinary tract infections (UTI) with *E. coli* during the first two years after transplantation. This microorganism was resistant to ampicillin, ciprofloxacin and trimethoprim-sulfamethoxazole. She received several courses of treatment with nitrofurantoin, cefazolin and cephalexin. She also developed 2 episodes of UTI with *Enterobacter aerogenes* which were treated with ciprofloxacin. This patient underwent investigation to rule out perirenal abscess. In 2013, following multiple episodes of urinary tract infections, the probable diagnosis of renal allograft abscess was made considering the result of computed tomography (CT) scan and technetium 99m white blood cell scan. The CT scan of kidney allograft showed an abnormal soft tissue density with perinephric fluid with a size of 6.6 cm x 5.2 cm in maximal axial dimension. It was difficult to differentiate between abscess and mass. However, the white blood cell scan suggested possible presence of an abscess at the superior aspect of the allograft. She underwent percutaneous drainage of the perinephric collection. Subsequently, the decision was made to obtain a kidney biopsy to rule out post-transplant lymphoproliferative disorder **(**PTLD). The percutaneous needle biopsy of the renal allograft revealed histologic characteristics that were consistent with malakoplakia without evidence of malignancy. There was a predominance of CD68-positive histiocytes containing abundant PAS positive granular material. There were also numerous pale concretions, which were positive for Von Kossa stain consistent with Michaelis Guttmann bodies (figure 1). Considering the result of biopsy, we modified immunosuppressive regimen as

follows: tacrolimus does were reduced to achieve through level of 3–3.5 ng/ml. We also decreased the dose of mycophenolic acid by 50 %. We also reduced the dose of prednisone to 5 mg/day. We started a course of oral antibiotic therapy including oral ciprofloxacin 250 mg twice daily and amoxicillin-calvulanic acid 250 mg-125 mg twice daily for two weeks. We closely monitored allograft function. Subsequently, we continued oral amoxicillin-calvulanic acid as chronic suppressive therapy and discontinued ciprofloxacin. We monitored all side effects while the patient was on antibiotic. The renal transplant patient did not experience recurrence of symptomatic urinary tract infection for at least 4 years. Multiple follow- up renal transplant ultrasounds and abdominal CT revealed slowly reducing of the size of malakoplakia lesion in the transplant kidney. The most recent ultrasound study in 2018 showed no malakoplakia lesion, fluid collection or abscess. Her most recent tests in 2018 showed stable renal function with maintaining serum creatinine at 70-80 µmol/L.

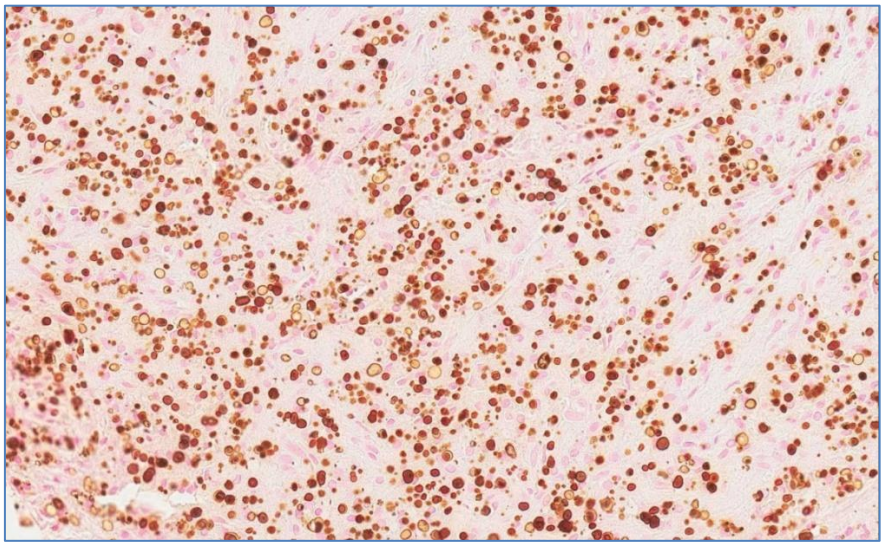

Fig-1: Von Kossa highlights intracytoplasmic (Michaelis Gutmann) bodies, a characteristic of malakoplakia

Case 2

A 62-year old female received renal transplant from a deceased donor in 2008. She did not undergo nephrectomy at the time of transplantation and her underlying renal disease remained unknown. She did not receive immunosuppressive medications prior to transplantation. She received induction immunosuppression with rabbit-antithymocyte globulin. She maintained on tacrolimus (target trough levels remained at 6-7 ng/ml in first year then 5 ng/mL after that), mycophenolic sodium and prednisone (titrating down to 15mg every other day). Postoperative course was complicated by delayed graft function. Her baseline serum creatinine level was 130 µmol/L. Six years later, her serum creatinine started to rise with a peak level at 278 µmol/L. She did not develop allograft rejection after transplantation. Multiple urine cultures did not reveal a pathogen and she remained asymptomatic. Ultrasonography and CT scan of transplant kidney were normal. A kidney transplant biopsy showed immunohistochemically evidence of malakoplakia including CD68 positive histiocytes (figure 2). Within the histiocytes there were PAS and Von Kossa positive intracytoplasmic bodies. In addition, it showed prominent neutrophilic casts raises the possibility of ascending infection. She received long-term antibiotic treatment associated with reducing the doses of the immunosuppressive medications. The dose of tacrolimus was decreased to achieve trough level of 3-3.5 ng/mL. We also decreased the dose of mycophenolic acid by 50% to 360 twice a day. We also reduced the dose of prednisone to 10 mg every other day. She initially received treatment with oral levofloxacin 250 mg Q48 and oral amoxicillin-calvulanic acid 500mg-125 mg twice a day for 6 months. Subsequently, we discontinued levofloxacin and continued treatment with amoxicillin-calvulanic acid. We repeated her urine culture every month for 6 months which all came back negative. The kidney function slowly improved with reduction of baseline serum creatinine. Her most recent tests in 2018 showed stable renal function with maintaining serum creatinine at 180-190 µmol/L. Graft function remained stable for the last three years.

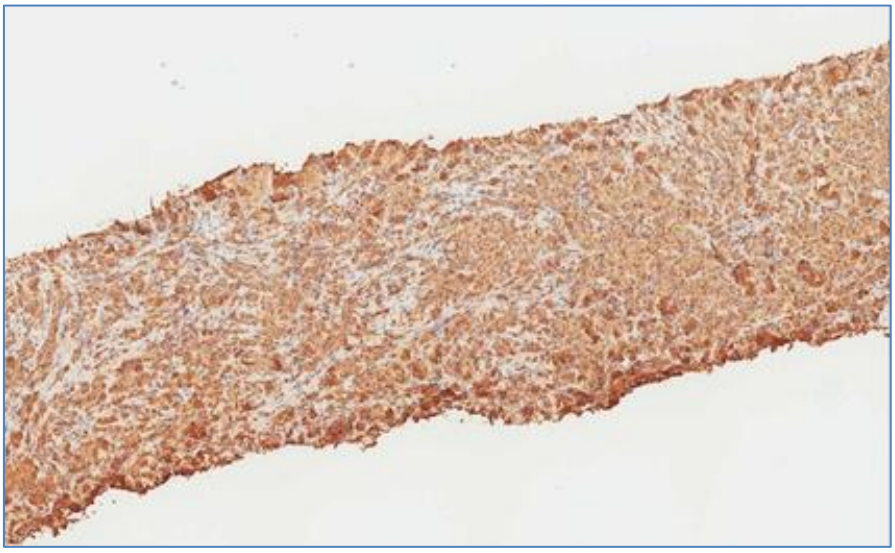

Fig-2: Renal biopsy shows abundant histiocytes, which are positive for CD68

DISCUSSION

Malakoplakia is a progressive disease with undetermined etiology. It mainly involves the genitourinary tract system. However, it has been reported to affect the skin, lungs, prostate and many other organs [3-6].

The most likely presentations of malakoplakia are recurrent urinary tract infection, acute kidney injury or both. E. coli is the most common microorganism that causes urine tract infection [5-7]. Other microorganisms have also been isolated [8]. Malakoplakia has been also shown to be associated with immunosuppression [1]. The cumulative immunosuppressive burden has been shown to be an important contributing factor for malakoplakia [9]. On the other hand, reducing of immunosuppression may cause improvement of malakoplakia. Biggar *et al*. demonstrated improvement of the phagocytic cell capacity after immunosuppressive therapy withdrawal [9-10].

The precise pathogenesis of malakoplakia is not entirely clear yet. Many theories explained different possible mechanisms for malakoplakia [8]. Severe suppression of cell mediated immunity including defect in macrophage function has been implicated in the pathogenesis. This defect leads to inability of monocytes and macrophages to digest the bacteria by phagocytosis. The defective lysosome function and low intracellular concentration of cyclic guanosine monophosphate (cGMP) in mononuclear cells are main abnormal functions of macrophages. This leads to calcified basophilic structures and the Michaelis-Guttmann- bodies which are the fundamental histologic pictures for diagnosis malakoplakia [5-9].

The most important entities in the differential diagnosis of renal transplant malakoplakia are xanthogranulomatous pyelonephritis and post-transplant lymphoproliferative disorder. The diagnosis of malakoplakia can be determined only by histopathological findings demonstrating cytoplasmic Michaelis-Gutmann bodies. These inclusion bodies are stained with Perl's stain, periodic acid-Schiff and von Kossa stain. Immunohistochemically studies also show CD68 positive histiocytes [3-9].

Although the radiological appearance of post-transplant malakoplakia is generally non-specific, the imaging studies may suggest its etiology and also guide the sampling. On ultrasound, the most common feature of post-transplant malakoplakia is a diffuse enlargement of affected allograft. Less frequently, hypoechoic lesions and increased echogenicity of the kidney parenchyma may be detected. Magnetic resonance imaging (MRI) may demonstrate multiple small low signal nodules and nephromegaly. Computed tomography (CT) may also show enhancing solid or cystic components and nephromegaly [11, 12].

Renal parenchymal malakoplakia is associated with an aggressive course and significant morbidity in kidney transplant patients [13, 14]. However, the outcome of post-transplant malakoplakia may improve with antibiotic therapy [7]. Although data related to the antibiotic treatment is limited, a good outcome may be achieved with immunosuppression reduction and administration of antimicrobial agents [5]. The antibiotics should penetrate the cell membrane and must have intracellular activity within the macrophages [8, 9]. Antibiotics other than the ones used in this study are trimethoprim- sulfamethoxazole (TMP-SMX) and gentamicin. There is no clear recommendation about the optimal duration for antibiotics regimen [7-12]. These therapeutic approaches to malakoplakia may improve patients and grafts survival. The aim of treatment is to augment macrophage function and facilitate host defense [7-15]. If the malakoplakia progresses, nephrectomy is required [14]. Both patients

explained in this study were successfully treated with reduction of immunosuppression and long-term antibiotic therapy.

We reviewed all kidney transplant patients with malakoplakia who were reported since 2000 (table 1). Transplant nephrectomy was needed in one patient due to multiple abscesses involving the graft [4]. All patients were on immunosuppressive therapy including mycophenolic acid and tacrolimus except for one patient that the authors did not explain the immunosuppressive regimen in detail [4]. Only one patient with malakoplakia was a kidney-pancreas recipient [16]. The antibiotic regimens and the duration of treatment were variable. However, all patients who received a long-term antibiotic therapy had successful outcomes with preserved allograft function.

Table-1: Review of case reports dealing with the management of malakoplakia in renal transplant patients

Studies	Age/sex	Time from transplant	Immunosuppression	Organism	Treatment /duration	outcome
Pusl *et al*. [5]	43/F	2 years	-Mycophenolic acid -Tacrolimus	E. coli	Antibiotic (not specified)/ Not mention duration	Cure
Puerto *et al*. [4]	45/F	2 years	Not specific	E. coli	Nephrectomy	Graft loss
Augusto *et al*. [3]	56/F	11 months	-Mycophenolate Mofetil -Tacrolimus	E. coli	-Decrease immunosuppression -Gentamicin for 3 days -levofloxacin for 10 weeks	Salt losing nephropathy
Honsova *et al*. [11]	31/F	3 years	-Mycophenolate Mofetil -Tacrolimus	E. coli and staphylococcus aureus	-Decrease immunosuppression -quinolone/ not mention duration	Cure
Graves *et al*. [9]	56/F	2 years	-Mycophenolate Mofetil -Tacrolimus -prednisolone	klebsiella pneumoniae	-Decrease immunosuppression -12 weeks intravenous piperacillin/tazobactam - oral faropenem and fosfomycin for 18 months	Cure
Neeto-Rios *et al*. [17]	45/F	2 years	-Mycophenolate sodium -Tacrolimus -Prednisone	E. coli	-Decrease immunosuppression -Surgery -TMP/SMX for 12 weeks	Cure

CONCLUSION

The current level of evidence for the management of malakoplakia is limited. Although this is a rare disease, malakoplakia should be considered in renal transplant patients presenting with graft dysfunction with or without recurrent urinary tract infection [17]. Although imaging studies are helpful for the diagnosis, kidney biopsy is still the gold standard method. Immunosuppression reduction and long-term antibiotic therapy decrease the size of lesions. Renal transplant nephrectomy must be considered for refractory cases [3-4]. More studies are needed to know the optimum duration of therapy.

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