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Teaching Point
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Renal allograft granulomas in the early post-transplant period

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Introduction

Granulomatous interstitial nephritis is an uncommon but potentially reversible cause of impaired kidney function. In the native kidney, granulomatous interstitial nephritis is commonly attributed to drug hypersensitivity, sarcoidosis, or tubulointerstitial nephritis and uveitis, with a significant fraction of cases labelled as 'idiopathic' [1]. In kidney transplant recipients, the incidence of interstitial nephritis has been reported to be <1% with only a fraction of these containing granulomas [2,3]. Although drug-related disease remains the most common aetiology of granulomatous interstitial nephritis, accurate diagnosis is particularly important in kidney transplant recipients due to concern over the consequences of altering immunosuppression in the early post-transplant period.

Few published reports have described the evaluation and management of granulomatous interstitial nephritis in kidney transplant recipients, particularly in the immediate post-transplantation period. In the following report, we present three patients with granulomatous interstitial nephritis presenting within 3 months of kidney transplantation. All three are unique in their clinical presentation, pathological features, and outcome. In describing the cases, we illustrate the complexity of this issue and describe a measured approach to the diagnosis and management of granulomatous interstitial nephritis post-transplantation.

Case 1

A 55-year-old Caucasian woman developed end-stage renal disease (ESRD) 11 years after liver transplantation. Her liver disease was from autoimmune hepatitis. She underwent deceased-donor kidney transplantation. She received rabbit anti-thymocyte globulin (rATG) for induction and continued mycophenolate mofetil, tacrolimus and prednisone for maintenance immunosuppression. Her initial course was uncomplicated with a decrease in serum creatinine concentration (SCr) from 6.7 mg/dL [510.9 mmol/L] preoperatively to 1.4 mg/dL [106.8 mmol/L] by post-operative Day 9.

She had a febrile episode accompanied by nausea on post-operative Day 4 which resolved spontaneously. On post-operative Day 9 she reported an increase in abdominal distention and lower extremity oedema bilaterally. Laboratory studies drawn at the visit were unchanged from previous visits. Her physical examination was consistent with volume overload, and an increased dose of furosemide was prescribed. Four days later ongoing lower extremity oedema, abdominal distention and weight gain (up 9 kg from dialysis dry weight) were noted. There was no evidence of uveitis, rash, fever, arthralgia, dyspnea, cough or haemoptysis. She had no recent travel history or known exposure to tuberculosis (TB). SCr was elevated at 2.3 mg/dL [175.4 mmol/L], and she was admitted for inpatient evaluation. A transplant kidney biopsy (Figure 1A) revealed granulomatous interstitial nephritis. There was no evidence of caseous necrosis and acid-fast bacilli (AFB), and Gomori-methenamine silver (GMS) stains were negative for mycobacteria and fungi, respectively. Vasculitis, crescentic glomerulonephritis or definite support for tubulointerstitial rejection was not seen. C4d stain (for evidence of humoral rejection), SV40 (for evidence of BK polyoma virus infection), herpes simplex virus 1 and 2 and adenovirus immunostains were all negative. Overall, a drug-induced process was favoured.

Urinalysis was negative for protein and showed transient haematuria, which cleared on repeat tests. Serum calcium concentration was within the normal range. The leukocyte count was also normal, with no eosinophilia. Multiple chest radiographs were unremarkable, with no findings suggesting TB, necrotizing granulomatous vasculitis or sarcoidosis. Serum Quantiferon test, urine stain and culture for AFB, and anti-neutrophilic cytoplasmic antibodies (ANCA) were sent.

Clinical course

Based on the clinical presentation, laboratory tests, imaging studies and transplant kidney biopsy, the likeli-

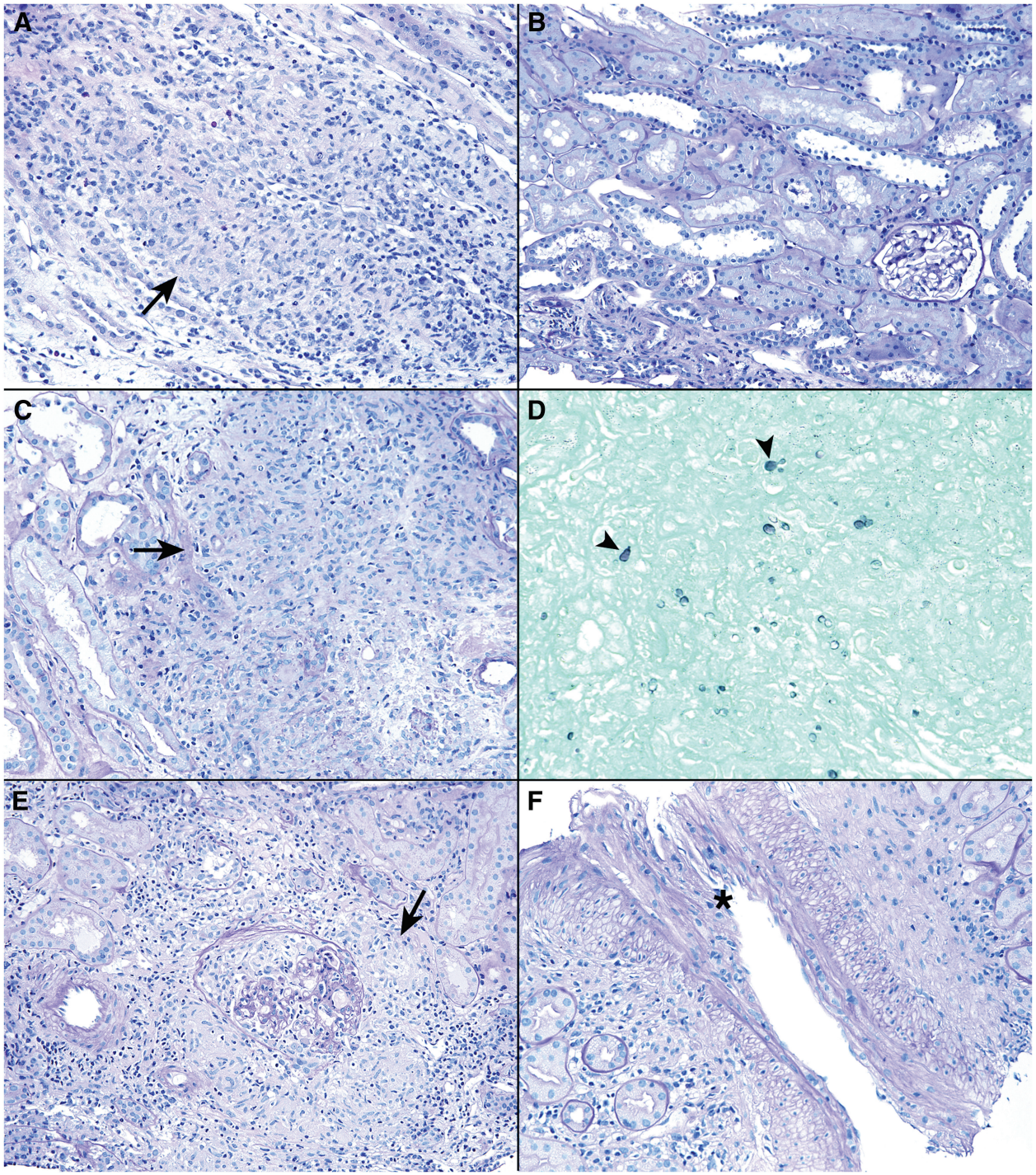

Fig. 1. Histological features of renal allograft biopsies. of case 1 (**A**,**B**), case 2 (**C**,**D**) and case 3 (**E**,**F**) (**A**) Ill-defined collections of epithelioid histiocytes are seen in the medulla, centred around the vasa recta (arrow). Patchy granulomatous inflammation was seen in the cortex as well, but there was no evidence of vasculitis, crescents or infectious aetiology. (**B**) The granulomatous inflammation completely resolved with corticosteroid therapy, as seen in a repeat biopsy performed 5 weeks later. (**C**) Renal allograft biopsy shows granulomatous tubulointerstitial inflammation (arrow). (**D**) A GMS stain revealed fungal yeast forms within the granulomas, measuring 5–10 μm in diameter and morphologically suggestive of *Histoplasma* species (arrow head). (**E**) The first biopsy revealed tubulointerstitial non-caseating granulomas and some were periglomerular, compressing the capillary tufts and disrupting the Bowman's capsules (arrow). There were no glomerular crescents or necrotizing lesions. (**F**) A repeat biopsy revealed intimal arteritis (asterisk) along with persistent granulomatous inflammation, raising the possibility of coexistent acute vascular rejection.

hood of infection was low. The biopsy result excluded the diagnosis of acute rejection. There was no evidence of sarcoidosis, with a normal serum calcium concentration and absence of nephrocalcinosis. Although she had a known history of autoimmune disease involving the liver, a previous native kidney biopsy showed no evidence of autoimmune disease or vasculitis. Serologic work-up, including ANCA, was negative. Despite this,

the recurrence of an undiagnosed primary disease remained a possibility.

Drug-induced interstitial nephritis was considered the leading diagnosis, and all potential offending medications were stopped on the day of admission. These included omeprazole, glipizide and trimethoprim–sulfamethoxazole. She was also placed on long-acting insulin for glycaemic control and inhalation pentamidine for *Pneumocystis carinii* pneumonia prophylaxis. In the absence of acute rejection, the main treatment dilemma was whether to treat with an increased dose of steroids. Although the biopsy did not stain for AFB or other microorganisms, the sensitivity is low, and waiting for the culture results would delay treatment if infectious causes were the inciting cause. Detailed information regarding the deceased-donor's infectious history and the clinical status of the recipient of the mate kidney revealed no evidence of unusual infections from the donor. She was treated with three doses of methylprednisolone 500 mg daily, followed by daily oral prednisone (60 mg). Upon discharge, she had continued improvement in her swelling and energy level, with corresponding improvement in her SCr to 1.0 mg/dL [76.3 mmol/L].

Repeat allograft biopsy, performed 5 weeks later, showed marked improvement in interstitial inflammation, with resolution of the granulomas (Figure 1B). Prednisone was tapered off.

Case 2

A 57-year-old Caucasian man with ESRD due to haemolytic uraemic syndrome with thrombotic thrombocytopenic purpura underwent living-unrelated kidney transplantation. He received induction immunosuppression with rATG and was maintained on tacrolimus, mycophenolate mofetil and prednisone. His operative course was uncomplicated, and he had excellent allograft function with an SCr nadir of 1.1 mg/dL [83.9 mmol/L].

His allograft function remained stable until ~1 month after transplantation, at which time his SCr rose to 2.4 mg/dL [183.0 mmol/L]. On physical examination, he was afebrile, normotensive and his allograft site was non-tender to palpation. Imaging studies of his allograft showed moderate hydronephrosis and he underwent double-J stent and nephrostomy tube placement. His SCr peaked at 5.9 mg/dL [449.9 mmol/L]. Despite structural decompression, SCr remained high, and transplant kidney biopsy revealed granulomatous interstitial inflammation with minimal necrosis (Figure 1C). An AFB stain was negative, but GMS stain revealed yeast forms morphologically suggestive of *Histoplasma* species (Figure 1D).

Clinical course

Based on his initial clinical presentation and preliminary biopsy results, this patient was thought to have eosinophilic granulomatous interstitial nephritis due to trimethoprim–sulfamethoxazole. Soon afterwards, however, histochemical staining revealed budding yeast forms, and serum and urine studies for histoplasmosis antigen and antibody were positive. His immunosuppression was decreased and he was placed on itraconazole. Studies for blastomycosis, cryptococcus and coccidiomycosis were negative.

SCr improved to 1.4 mg/dL [106.8 mmol/L] and the nephrostomy tube was removed. Imaging studies showed evidence of a urethral stricture, for which he is scheduled to undergo repair.

Case 3

A 50-year-old African American man with type 1 diabetes mellitus and ESRD underwent simultaneous kidney and pancreas transplantation. His operative course and immediate post-operative course were uncomplicated. His immunosuppression consisted of mycophenolate mofetil, tacrolimus and a prednisone taper over 6 months. Preoperative SCr was 9.05 mg/dL [690.2 mmol/L] with a nadir of 0.99 mg/dL [75.5 mmol/L].

Six weeks after transplantation he was noted to have an asymptomatic rise in his SCr to 2.5 mg/dL [190.7 mmol/L]. He had no uveitis, rash, fever, arthralgia, purpura or pulmonary symptoms such as shortness of breath, cough or haemoptysis. Physical examination was normal.

All possible culprit drugs, including lisinopril, metoclopramide and ferrous sulphate, were discontinued. A serologic work-up was initiated, including serum antinuclear antibodies, double-stranded DNA antibodies, ANCA and anti-glomerular basement membrane antibodies (anti-GBM). Because of concerns for acute rejection, he was empirically placed on corticosteroids and transplant kidney biopsy was performed. The biopsy revealed several interstitial non-caseating granulomas, some of which were in a periglomerular distribution, with disruption of the Bowman's capsules (Figure 1E). Crescents, viral inclusions or vasculitis were not identified. AFB and GMS stains and C4d immunostain were negative.

A repeat biopsy was performed 2 weeks later, which showed similar glomerular and tubulointerstitial histology. In addition, several cross sections of arcuate and interlobular calibre arteries had mild to moderate intimal arteritis (Figure 1F), worrisome for acute vascular rejection (Banff grade IIa). Overall, the aetiology was unclear and the differential diagnosis included infection, drug reaction, necrotizing granulomatous vasculitis and acute vascular rejection.

Clinical course

The aetiology of granulomatous interstitial nephritis in this patient was unclear. Despite stopping all possible offending agents and empiric treatment with corticosteroids, the SCr continued to rise, up to 5.05 mg/dL [385.1 mmol/L] 2 weeks after the first transplant kidney biopsy.

Both the initial and follow-up biopsies showed evidence of vasculitis and periglomerular granulomatous inflammation. The biopsy results plus uncertainty regarding the exact nature of his primary disease raised the possibility of recurrent glomerulonephritis. However, serologic work-up for pauci-immune glomerulonephritis and GBM antibody-

Table 1. Reported cases of granulomatous interstitial nephritis in the transplant allograft

	Time post-transplant	Probable aetiology	Clinical outcome
Lapasia *et al*.	9 days	Drug-induced	Functioning allograft, SCr 1.0 mg/dL [76.3 mmol/L]
	4 weeks	*Histoplasma*	Functioning allograft, SCr 1.4 mg/dL [106.8 mmol/L]
	6 weeks	Unknown	Lost allograft, resumed dialysis
Meehan *et al.* [3]	34 days	*C. albicans*	Transplant nephrectomy, fungal organisms on biopsy
	7 months	*M. tuberculosis*	Functioning graft, SCr 2.2 mg/dL [167.8 mmol/L]
	24 months	*E.coli*	Transplant nephrectomy, acute rejection
Ozdemir *et al.* [4]	[a]	*M. tuberculosis*	[a]
	[a]	*M. tuberculosis*	[a]
	[a]	*C. albicans*	[a]
Josephson *et al.* [2]	24 months	Drug-induced	Initially functioning allograft, SCr 1.9 mg/dL [144.9 mmol/L]; subsequently lost to severe acute rejection

[a]Not specified.

mediated disease was negative. Although his pancreas allograft continued to function well, his kidney function progressively worsened, and he was reinitiated on haemodialysis soon thereafter.

The recipient of the mate kidney had prolonged delayed graft function, subsequently dying within 3 months of transplantation. Patients receiving other mate organs (including liver, lung and intestine) have been reported as doing well without impaired organ function.

Discussion

We found limited literature addressing the evaluation and treatment of granulomatous allograft disease presenting soon after transplantation. Meehan *et al.* have previously reported an incidence of granulomatous interstitial nephritis in the allograft of 0.6% [3]. All three cases were attributed to infection (Candida, Mycobacterium) or treatment with antibiotics (Table 1). Similarly, a study of all allograft biopsies over a 3-year period showed a 1% incidence of granulomatous interstitial nephritis, with all three cases related to fungal or mycobacterial infections [4]. Here, we describe three unique cases of allograft granulomatous interstitial nephritis, which presented within 3 months after transplantation.

Studies of native kidney biopsies with drug-related granulomatous interstitial nephritis show the development of granulomas 4–10 weeks after the initiation of drug therapy [5]. Reports of drug-related interstitial nephritis in the allograft show a more variable time course, with cases presenting anywhere from Day 8 to Day 720 post-transplantation [2,3]. Although almost all drugs can cause hypersensitivity reactions, the most common culprits in interstitial nephritis are non-steroidal anti-inflammatory drugs, antibiotics (penicillins, cephalosporins, rifampin, quinolones), sulfonamides, allopurinol, and proton pump inhibitors [6]. Importantly, the development of a reaction is not dose-dependent and recurrence or exacerbation can occur with a second exposure to the same or a related drug.

Although it can also have a widely variable time course, tuberculous disease in the renal allograft rarely occurs within the first month of transplantation, especially in low-risk patients from non-endemic areas and in the absence of pre-existing mycobaterial disease or donor disease [7,8]. In our Case 1 patient, serial pre-transplantation chest radiographs and PPD skin tests were negative. She did not have known prior infection or exposure to TB and did not live in a TB-endemic area. Investigation of the donor revealed no evidence of latent or active mycobacterial disease. Additionally, the patient receiving the mate kidney had stable allograft function with an SCr of 0.8 to 1.2 mg/dL [61.0 to 91.5 mmol/L], and no evidence of mycobacterial disease.

Interstitial inflammation is often a key feature of acute allograft rejection. However, we found no reports showing a clear association between granulomatous interstitial nephritis and acute rejection without a coexisting condition to explain the granulomas. Banff 97 guidelines for grading allograft rejection also do not indicate granulomas as a component of rejection [9].

All three of the cases described in our report had unique clinical characteristics and pathological features on allograft biopsy. In Case 1, the patient presented with granulomatous interstitial nephritis on biopsy which was ultimately attributed to drug hypersensitivity, and which responded to corticosteroids. In Case 2, the patient also presented with granulomatous interstitial nephritis, this time related to fungal infection. In Case 3, the patient presented with granulomas in a periglomerular distribution, with unclear underlying aetiology, and no response to corticosteroids.

These cases illustrate the diversity of diagnoses associated with granulomatous interstitial nephritis in kidney transplant recipients. The management of this pathologic finding is particularly challenging in this population as they are susceptible to both rejection and infections. Because the consequences can be particularly severe and time-sensitive, it is important to follow a streamlined approach in the diagnosis and management.

The first step should be to stop potentially offending drugs and any other non-essential exposures such as over-the-counter agents and supplements. As culture results can take days to weeks to return, it is also critical to initiate the evaluation for bacterial, fungal and mycobacterial infections early on. Because of the vastly different treatment regimens for infection versus rejection, it is important to consider specific recipient risk factors such as sensitization and prior immunosuppression. Particularly in deceased-donor transplantation, the source of the organ,

donor risk factors for infection and the function of other donated organs from the same source can also provide key clues to the underlying disease process. Although uncommon, sarcoidosis should be considered, especially in the presence of hypercalcemia or systemic findings such as pulmonary opacities or skin lesions. Because sarcoid-associated granulomas in the kidney show a high sensitivity to corticosteroids, early detection and treatment can lead to remarkable improvement [10]. If there is a low suspicion for infection and initial work-up is negative, low-dose corticosteroid treatment should be initiated. If the granulomas are found in a periglomerular distribution, a detailed clinical history, examination and serologic evaluation for vasculitis should be performed, including ANCA and anti-GBM antibodies.

Teaching points

(1) Granulomatous interstitial nephritis can occur early in the post-transplantation period.

(2) Therapy should be initiated based on clinical suspicion after considering both donor and recipient risk factors.

(3) If granulomatous interstitial nephritis is observed in this setting, all possible culprit drugs should be stopped, an infectious evaluation should be initiated and there should be a low threshold for repeat biopsy.

(4) An increase in immunosuppression should be considered only when the suspicion for infectious aetiologies are low or excluded.

Conflict of interest statement. None declared.

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