

In-Depth Clinical Review

Make the grade for Wegener's granulomatosis after kidney transplantation

Lioba Schewior¹, Duska Dragun¹, Birgit Rudolph² and Elke Schaeffner¹

¹Department of Nephrology and Intensive Care Medicine, Charité Campus Virchow and ²Department of Pathology, Charité Campus Mitte, Berlin, Germany

Abstract

Antineutrophil cytoplasmic antibodies-associated vasculitis (AAV) is a well-described cause of multiple organ involvement including rapidly progressive pauci-immune crescentic glomerulonephritis. Kidney transplantation (KTx) is considered the treatment of choice in patients with end-stage renal disease (ESRD) due to AAV. Patient and graft survival in AAV after KTx is favourable and comparable with other non-diabetic causes of ESRD. While relapse of AAV is high in dialysis patients (up to 50%), it decreases after KTx (8.6–22.2%). Yet, relapse may occur at any time after KTx and transplant involvement has been documented in at least 25 cases. Therapeutic guidelines for the management of AAV after KTx do not exist and clinical management is a controversial discussion. We present two unusual cases of young males with smouldering AAV who recently underwent KTx at our hospital. Case 1 experienced repeated relapses after KTx and was finally successfully treated with rituximab. Case 2 received rituximab pre-emptively before living kidney donation and remained free of flairs. Prompted by these two cases, we reviewed the literature focusing on the right point of time for transplantation, risk assessment, role of antineutrophil cytoplasmic antibodies, clinical presentation of flairs and immunosuppression in smouldering Wegener's granulomatosis (WG) and in relapse, including individualized treatment with rituximab.

Keywords: ANCA; kidney transplantation; relapse; rituximab; vasculitis

Recurrence of Wegener's granulomatosis

Although end-stage renal disease (ESRD) due to antineutrophil cytoplasmic antibodies-associated vasculitis (AAV)

is a rare event with five cases per million per year, there is upcoming recognition of kidney transplantation (KTx) and the risk of relapse in this disease [1–3]. Reports of relapse rates, individual organ involvement and general severity of AAV after KTx provide variable results. There are a number of published case reports indicating that KTx is an excellent treatment option in patients with AAV who reached ESRD [4,5]. Results from the Collaborative Transplant Study which included 387 patients describe a 10-year patients' and graft survival rate of 80% and 65%, respectively — a result same as or even better than in patients with other causes of ESRD (e.g. 70.9% in polycystic kidney diseases) [6]. Similar data are described in a study by Allen *et al.* with a 5-year patient and graft survival of 85% and 69%, respectively [7]. Even if reports of relapse rates of AAV after KTx vary largely, overall studies have shown that relapse in kidney transplant recipients (KTR) with Wegener's granulomatosis (WG) is significantly lower than that in dialysis patients (0.02–0.1 versus 0.09–0.3 relapses/patient/year) [3,8]. In most recent series, relapses occur <10% in patients receiving induction therapy in conjunction with a calcineurin inhibitor, mycophenolate mofetil (MMF) and methylprednisolone (Pred).

An unusual case attracted our attention, of a 42-year-old patient with a 5-year history of recurrent WG with pulmonary infections who underwent KTx in the state of smouldering disease. Under 'standard' immunosuppressive treatment, he was experiencing two episodes of relapsing WG affecting his lungs and his kidney transplant. And there was the second case of a 28-year-old patient with a history of severe, recurrent pulmorenal WG and smouldering disease despite repeated cycles of CYP. He finally received two cycles of rituximab before living donor KTx had been carried out and has remained free of flares so far. Along the management of these 'index cases', several questions concerning WG in KTR were brought up and shall be discussed with respect to the literature: the right point of time for transplantation, the role of antineutrophil cytoplasmic antibodies (ANCA), the pre-transplantation risk assessment, the clinical presentation of flairs, the immunosuppressive regimen in patients with smouldering WG and treatment of relapse.

Correspondence and offprint requests to: Duska Dragun, Department of Nephrology and Intensive Care Medicine, Charité Hospital, Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49-30-450-653485; Fax: +49-30-450-553909; E-mail: duska.dragun@charite.de

Point of time for KTx in smouldering disease

Although it has never been formally studied, there is common belief that KTx in WG is favourable when the patient is in stable remission [9,10]. In the case of transplantation from deceased donors the 'optimal' point of time for KTx is not foreseeable and thus cannot be planned. The question of whether it is advisable to transplant a patient in a state of smouldering disease or to wait until he is in clear remission is not really answered in the literature. In a pooled analysis of 127 patients, the duration of dialysis prior to transplantation did not affect subsequent relapses [10].

The clinical value of ANCA

Early evidence about the usefulness of ANCA as markers of clinical activity in WG dates back to 1985 [11]. In the generalized form of WG, PR3-ANCA are seen in 70–80% and myeloperoxidase ANCA (MPO-ANCA) in 10% of patients. In limited WG, ANCA are detected in only 60% of cases [12]. However, the predictive value of elevation in ANCA levels for pre-emptive treatment of relapse in WG remains questionable. Fifteen mostly retrospective studies attempted to calculate the number of AAV patients who developed a relapse after a rise in ANCA titres. Analysing these reports, 25–42% of patients did not have a relapse despite elevated ANCA titres [13]. Thus, for WG the evidence to help balance risk and benefit of a pre-emptive treatment for relapse does not exist, as ANCA titres alone do not seem a valuable tool for guiding treatment.

Furthermore, in KTR the role of ANCA as a predictor of relapse has been a matter of controversy. Several groups have reported successful KTx without relapse in WG despite the evidence for ANCA at transplantation [14,15]. In another case series, 7 out of 30 KTR with WG had positive ANCA titres and only one of them suffered from recurrence, indicating no difference in relapse rates between patients with and without detectable ANCA titres at the time of KTx [16]. In a pooled analysis of 127 patients with AAV of whom 39 were known to have circulating ANCA at the time of transplantation, recurrent disease occurred in 10 patients, corresponding to a relapse rate of 25.6%. There was no statistically significant difference to those without circulating antibodies, postulating that the presence of a positive ANCA at the time of transplantation should not preclude transplantation [10]. However, information regarding ANCA titres had only been available in a minority of the observed population (39 out of 127) and conclusions from subgroup analysis should be drawn with great caution and substantiated in prospective studies. In addition, it should be kept in mind that even under optimal conditions, the inter-centre coefficient of variability for ANCA testing still amounts to 15–35% [17].

On the other hand, in some settings ANCA serologies may provide valuable information about disease activity. In one prospective study of 33 patients who suffered from disease relapses, only two patients showed no preceding rise in ANCA titre (both having persistently high ANCA levels, even during remission) [18]. Another study demonstrated

that PR3-ANCA levels >10 U/mL at 18 and 24 months were predictive of relapse within 5 years after treatment [19].

Thus, although the value of routine ANCA measurement pre- and post-transplantation may not be reliable, their identification seems to be common practice in most clinical settings. Despite the contradicting study results, the clinical use of ANCA as a marker of disease activity and as early predictors of relapse might still have important value. Yet we feel that this value should inseparably be associated with the concurrent additional measurement of CRP levels and conscientious recognition of clinical symptoms. In the index cases with smouldering disease in which KTx was carried out despite positive ANCA titres, quantitative follow-up measurements were performed regularly.

Risk assessment for relapse in patients waiting for a transplant

Estimating the risk of relapse in a patient with WG is important in order to choose a treatment concept after KTx. According to a relatively huge prospective cohort analysis that followed 350 patients with AAV for 4 years, the following factors were associated with relapse in 258 (77%) patients who had attained remission: seropositivity for PR3-ANCA and disease of the lung or upper respiratory tract. Relapses occurred in only 26% of patients with no risk factors and 73% of patients with all three risk factors corresponding to a 3.7-fold increase in risk for relapse compared to patients with none of these risk factors ($P = 0.007$). Hereby, patients with PR3-ANCA-associated vasculitis were found to be more prone to experiencing relapse than MPO-ANCA-positive patients [20]. Due to these study results, positive PR3-ANCA titres during early follow-up identified patients at increased risk of relapse. Yet another, albeit retrospective study showed that patients who remained persistently negative for PR3-ANCA after induction of remission had a reduced risk of relapse [19]. Even though these analyses are precious, similar data on patients after transplantation are scarce and difficult to achieve due to the small number of patients experiencing relapse after KTx. However, the reported two index cases revealed positivity for all risk factors described above at the time of transplantation. Hereby, the index case 1 underwent repeated flares under standard therapy while index case 2 remained free of relapse after pre-transplantation rituximab therapy.

In conclusion, a multi-modal approach, taking into account the patients' history for relapse risk assessment, laboratory measurements and clinical presentation, might be favourable in the detection of relapse of WG in KTR.

How do recurrences of WG present clinically in a KTR?

Typical clinical presentation of WG is characterized by a rapid onset of glomerular haematuria, haemoptysis and nasal mucosal involvement, occasionally with cutaneous vasculitis. In contrast, symptoms at relapse after KTx vary

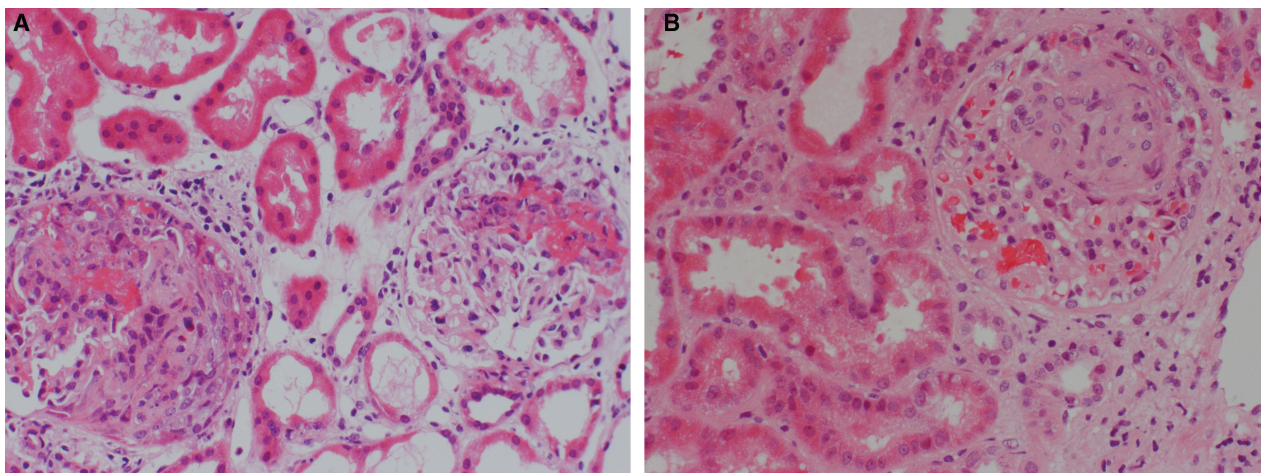


Fig. 1. Light-microscopic observation of crescentic glomerulonephritis in recurrence of AAV. (A) 6 months after KTx: two glomeruli showing moderate-to-severe extracapillary proliferation with marked fibrinoid necrosis. Fibrocellular crescent formation affected 70% of glomeruli. (B) Follow-up biopsy 4 weeks after treatment with PPH, CYP and Pred: a delineated segmental area of incipient glomerular sclerosis along the Bowman's capsule is present suggesting a reparative process of the necrotizing extracapillary lesion. Crescents are detected in the 20% of the glomeruli and 10% show glomerular sclerosis.

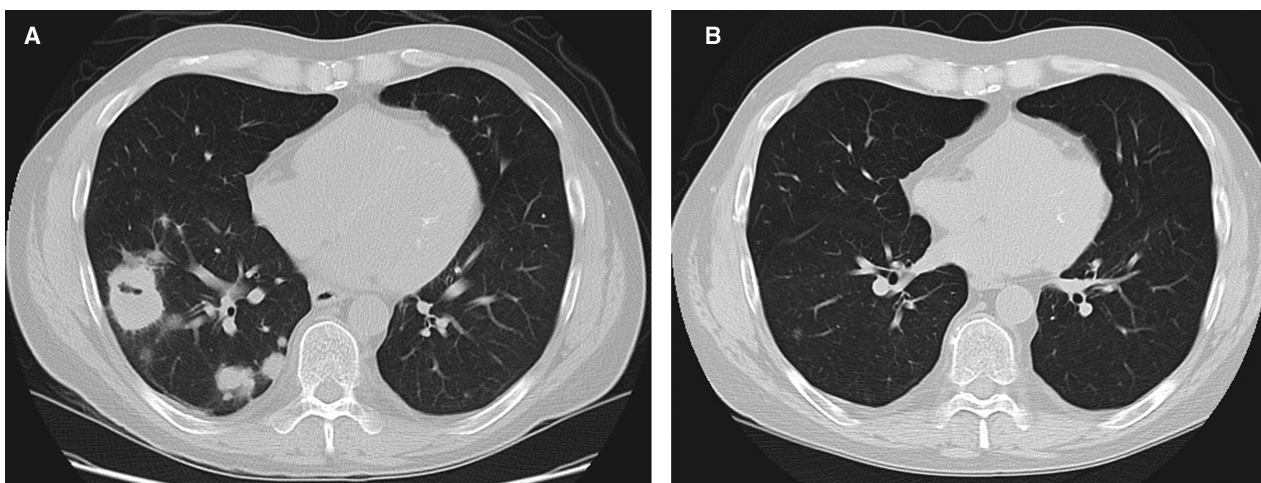


Fig. 2. CT-scan in a patient with concealed relapse of pulmonary Wegener's granulomatosis. (A) 6 months after KTx presenting with mild dyspnoea, microscopic haematuria: typical radiological manifestation of pulmonary WG with smooth and speculated nodules in the upper-right lobe. Cavitations are characterized by walls and partially shaggy, irregular inner borders. (B) Follow-up CT-scan 6 weeks after the second relapse of AAV and treatment with PPH, CYP and consecutively rituximab: discrete residual bilateral granuloma. The areas of consolidation are seen in association with small pulmonary nodules and foci of calcification.

widely with respect to onset, severity and organ involvement. Reports by Haubitz and Gera describe affection of the eyes as well as arthralgia and rash in some patients, while all of them had mild general symptoms with manifestation of the upper respiratory tract without KTx involvement [1,14]. Another case reported a catastrophic onset of relapse with KTx failure [21]. In our first index case, the patient presented with mild arthralgia 5 months after KTx, while imaging and histology revealed relapse of WG with renal and pulmonary involvement (Figures 1A and 2A). As shown here, the discrepancy between mild clinical symptoms and severe organ affection can be striking and the clinical differentiation between relapse and 'smouldering' disease even impossible. Hence, mild dyspnoea and microscopic haematuria seem to be the predominant symptoms

of relapsing WG after KTx, but other individual symptoms such as arthralgia, bursitis, granular tissue and erythema can also predict disease activity [22].

Immunosuppressive therapy after transplantation in WG

As a matter of fact, the choice of immunosuppressive therapy is a balancing between risk and benefit, notably in WG. Less immunosuppression decreases the likelihood of infection, but also the chance of suppressing the vasculitis, whereas heavy immunosuppression clearly increases the chance of having control over vasculitis and rejection

for the cost of a possibly life-threatening bacterial, fungal and opportunistic viral infection. Besides this, there is clear evidence that the incidence of polyoma virus-associated nephropathy, leading to KTx failure in ~40%, depends on the level of immunosuppression [23]. Furthermore, the incidence of malignancies increases with the net state of immunosuppression. In a retrospective study with a follow-up of 5 years, it could be shown that particularly KTR with pauci-immune SVV developed significantly more malignancies, most notably skin cancer [24].

While in earlier studies KTR on CyA failed to show a lower relapse rate than KTR on AZA [10], new data support the impression that modern immunosuppression including induction therapy, Tacrolimus (TAC) and MMF is favourable with a relapse rate in the TAC-based regimen of 4% ($n = 24$) and 22% in the CyA-based regimen ($n = 9$) [1]. Especially, MMF has been shown to be advantageous in these cases and should be part of every immunosuppressive regimen in KTR with AAV according to a review by Schmitt and van der Woude [9]. Literature, even though very limited, states that there is no difference in relapse rates when induction therapy prior to KTx is given (basiliximab, daclizumab, ATG, alemtuzumab, no induction) [9,25]. Bearing in mind the multiple infections in the past and the risk for new infections in a KTR with vasculitis [26], the chosen immunosuppressive regimen of the index case 1 consisted of CyA, MMF and Pred but no additional treatment with CYP in the early post-transplantation period. Retrospectively, according to the literature, a regimen including TAC as well as MMF would have rather been the favourite choice in a patient having experienced multiple relapses. In contrast, case 2 with a similar risk profile as case 1 received rituximab pre-transplantation, basiliximab as induction therapy and TAC as well as MMF and Pred as maintenance regimen and remained free of recurrence until now, 8 months post-transplantation.

As the risk of post-transplant CMV and polyoma infection due to immunosuppression in our index patients was increased notably, a Valganciclovir prophylaxis had been performed for 6 months. MV-APPAP titres were monitored monthly as well as urine cytology for polyoma BK virus every 3 months for the first year. In the case of a positive cytology, it was repeated within 1 month. Also a blood test for viraemia was done, followed by a renal biopsy in the case of a positive result.

To make the grade for the main risk of post-transplant malignancies including skin cancer, one of the major prevention strategies consists in pre-transplant education of skin protection and regular consultation by a specialized dermatologist. Furthermore, yearly physical examinations including a chest x-ray, abdominal and retroperitoneal ultrasound (with special focus on renal cell carcinoma and lymphatic disease), urine cytology, complete blood count, chemistry and viral serology should be performed.

What is the treatment of choice if relapse occurs?

Cycles of Pred as well as CYP are known to be effective for WG recurrence, and plasmapheresis therapy can be added when pulmonary involvement and high titres of

ANCA are present. Accordingly, case series demonstrate a generally good response to CYP for the treatment of relapse [14,27–29]. Still these reports show a high variety in respect of the severity of relapse, the affected organ, kind of immunosuppression at the time of recurrence and the treatment induced. Moreover, experience in dosing and dosing interval in treatment of AAV is limited. Unfortunately, several modern biological therapies with selective targets such as TNF inhibitors have failed to influence the course of AAV successfully and have usually been associated with loss of KTx function. This poor outcome underlines the need for new therapeutic strategies and the need to focus on pathophysiology and the role of ANCA, T and B cells in WG.

In addition to the role of ANCA inducing a necrotizing vasculitis by inciting a degranulation of leukocytes, multiple other elements of the immune system participate in the pathophysiology of WG. The autoantibody response that produces ANCA probably follows the exposure of a cryptic epitope. This antibody response may then generalize to the rest of the molecule by epitope spread. This hypothesis implies the role for T cells in the pathogenesis of the AAV. Moreover, most patients with ANCA-associated vasculitis produce isotype-switched immunoglobulin G ANCA, implying a secondary immune response driven by T cells [30]. Furthermore, according to Abdulahad, functionally defective T_{reg} cells influence the development and relapsing course of PR3-AAV [31]. In a cytometric assessment of patients with WG, T-cell activation persisted during remission of disease, while B-cell activation was related to active disease [32]. For the treatment of difficult-to-treat auto-immune diseases including AAV, there is upcoming evidence for the effectiveness of the monoclonal anti-CD-20 antibody rituximab [33,34]. Acting depletory on B-lymphocytes, rituximab has been used effectively off-label for patients with AAV refractory for CYP [35] and in refractory WG after KTx [36].

While the use of rituximab in the therapy of KTR has increased due to the well-described efficacy in the life-threatening post-transplant lymphoproliferative disorder (PTLD), there is now some concern about efficacy and safety in KTx after WG. In a recent report by Ferraro *et al.*, rituximab treatment was followed by effective peripheral B-cell depletion in a patient with WG, whereas in the tissue at sites of active disease there were still CD20(+) B cells to be found. This finding did correspond to a clinical relevant relapse of WG in this patient [37]. Furthermore, it should be mentioned that progressive multifocal leukoencephalopathy (PML) caused by reactivated JC-virus has been previously described in association with rituximab treatment [38] especially in patients with rheumatic disease and SLE [39]. According to the FDA Health Advisory, patients have to be informed about the risk of PML and the lack of effective treatment for PML before use of rituximab.

Currently, there is a randomized trial under way, comparing rituximab and CYP in non-transplant patients with AAV [33]. In the reported index case 1 with repeated relapse of WG after KTx and predisposition to leucopenia, rituximab was used as a rescue therapy. Applying a standard lymphoma regimen for single-agent rituximab use with a weekly dosing schedule of 375 mg/m² for 4 weeks [33], a

sustained treatment response could be reported 8 months after treatment (Figures 1B and 2B). In index case 2, the rituximab therapy was started electively pre-transplantation and included two rituximab infusions (375 mg/m² on days 28 and 14 pre-transplantation). Utilizing a larger dosing interval was followed by treatment failure in a case report by Omdal *et al.* [40]. According to several case series of refractory, WG treatment with rituximab seems to be faster and more successful in patients with predominantly vasculitis disease, as opposed to granulomatous manifestation [41–43]. Bearing in mind that relapse and opportunistic infection might occur repeatedly and silently, a more frequent clinical follow-up including a neurologic evaluation (for early signs of PML) of every 3 to 4 weeks as implemented in our cases might be recommendable.

Synopsis and conclusion

The optimal timing for KTx in patients with ESRD and WG remains open to debate. Although the presence of positive ANCA should not preclude transplantation [10,44], the prediction and avoidance of relapse is difficult when patients present with smouldering disease at the time of transplantation. Therefore, a multi-modal risk assessment including patient's medical history, ANCA and CRP measurements and clinical signs is favourable. While smouldering disease itself should not contraindicate KTx, immunosuppressive therapy in a patient should be chosen carefully and regimens including TAC and MMF may be preferred [1,17].

Hereby, it is of relevance that maintenance immunosuppression by itself in the form of a standard triple medication is not protective to prevent vasculitis relapse. Clinical signs of recurrence of WG after KTx might be atypical and ANCA titre and PR3-ANCA status can remain negative, facts that put even more emphasis on the great caution with which clinical presentation, CRP and urinalysis in a WG patient should be assessed. In conclusion, in KTR with WG, it seems to be crucial to perform risk assessment and to individualize immunosuppressive regimen as well as treatment of relapse taking into account alternative therapeutic regimens such as e.g. rituximab.

Conflict of interest statement. None declared.

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