

The clinical challenge of treating lupus nephritis

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Received for publication: 24/06/2008

Accepted in revised form: 05/12/2008

ABSTRACT

Lupus nephritis is a frequent manifestation of systemic lupus erythematosus and a key factor in systemic lupus erythematosus morbidity and mortality. The case of a young female patient with systemic lupus erythematosus is presented. The patient showed severe renal involvement, refractory to conventional immunosuppression (cyclophosphamide, corticosteroids, mycophenolate mofetil and ciclosporin), with need for alternative therapy (gamma-globulin, rituximab) and rapid progression to end-stage renal disease, complicated by persisting extrarenal lupic manifestations and problems with renal replacement therapies.

Key-Words:

Active lupus nephritis; alternative immunosuppression; conventional immunosuppression; dialysis; transplantation; systemic lupus erythematosus.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune chronic inflammatory disease of unknown aetiology which can affect several organs and systems. This disease is characterised by a variable course with acute and remission phases requiring prolonged immunosuppression therapy.

Lupus nephritis (LN) is a frequent, serious manifestation of SLE and the most important predictive factor in SLE morbidity and mortality. Although the

overall prognosis has improved, progress to renal failure still occurs in a significant percentage of cases and it is usually accompanied by a decrease in lupic disease activity¹.

Lupus nephritis forms refractory to conventional immunosuppression therapy represent an important challenge in daily clinical practice. A particularly aggressive case is presented, with a hectic activity and rapid progression to end-stage renal disease (ESRD), despite intense immunosuppression treatment. The authors discuss the dilemma of induction and maintenance treatment of this severe form of LN and the problems associated with the different renal replacement modalities, as renal failure in this case was not followed by burn-out of lupus activity.

CASE REPORT

A 26 year-old Caucasian woman born and living in a suburban milieu, with a 6-year SLE history beginning in 2002.

On diagnosis, she presented with eight of the eleven SLE criteria established by the American College of Rheumatology²: malar rash, photosensitivity, mouth ulcers, haematologic abnormalities (haemolytic anaemia and leucopenia), arthritis, nephritis (asymptomatic haematoproteinuria) and testing positively for ANA, anti-dsDNA and anti-sDNA autoantibodies. In addition, anti-SSA and anti-histone circulating antibodies were found. The first renal biopsy, performed three months after diagnosis,

showed diffuse proliferative glomerulonephritis (GN) (LN class IV-B, according to the 1995 World Health Organization [WHO] classification³), with segmental crescents and fibrinoid necrosis lesions on light microscopy (Fig. 1) and full-house glomerular deposits on immunofluorescence. Induction corticoid therapy was started at once (intravenous [IV] methylprednisolone 500 mg for 3 days, followed by a 1 mg/kg/day oral dose) and IV cyclophosphamide (CYC) for 18 months (0.75 g/m² of body surface area, in a regimen of 6 monthly pulses and 4 maintenance pulses every three months, with a cumulative 10 g dose). Partial clinical and serological remission was achieved.

Subsequently, the clinical course was characterised by frequent development of severe renal flares, with mixed manifestations of nephritic and nephrotic syndrome requiring adjustment of maintenance therapy. The first renal flare occurred 4 weeks after the last cyclophosphamide pulse (19 months after diagnosis), with nephrotic syndrome, non-oliguric acute renal failure (presenting an abrupt rise in serum creatinine from the baseline 0.9 to the worst level of 1.9 mg/dl), hypertension and symptomatic normochromic normocytic anaemia. A further renal biopsy showed endo- and extracapillary diffuse proliferative GN, with intense active lesions associated with chronicity lesions

(LN class IV-C). Intravenous corticoid pulses (methylprednisolone 1 g for 3 days) were instituted in association with mycophenolate mofetil (MMF) 2 g/day, with partial remission of the clinical features and renal function stabilisation to a serum creatinine level of 1.4 mg/dl. Four months later, after a febrile leucopenia episode accompanied by frank nephrotic syndrome, MMF was replaced with ciclosporin 5 mg/kg/day. The third renal flare with chronic kidney disease (CKD) acute deterioration with oliguria and severe hypertension occurred 28 months after diagnosis. The third renal biopsy also showed class IV-C LN, with frank signs of activity (endo- and extracapillary diffuse proliferation) on a chronicity background (focal and segmental glomerular sclerosis and chronic interstitial nephritis with mild fibrosis and tubular atrophy). After pulsed IV methylprednisolone infusions (1 g for 3 days), the maintenance therapy was then converted to higher dose MMF, 3 g/day. The fourth serious renal flare within a year (involving an active LN with predominance of chronicity lesions [class IV-C evolving to class VI] on the fourth renal biopsy – Fig. 2) associated with refractoriness to conventional immunosuppressant therapy led to the decision to initiate intravenous gamma-globulin therapy (IVIg). Eleven IVIg 400 mg/kg/day cycles were performed, for 4 days in the first three cycles and then 1 day treatment every 3 weeks. During the 11 months under this

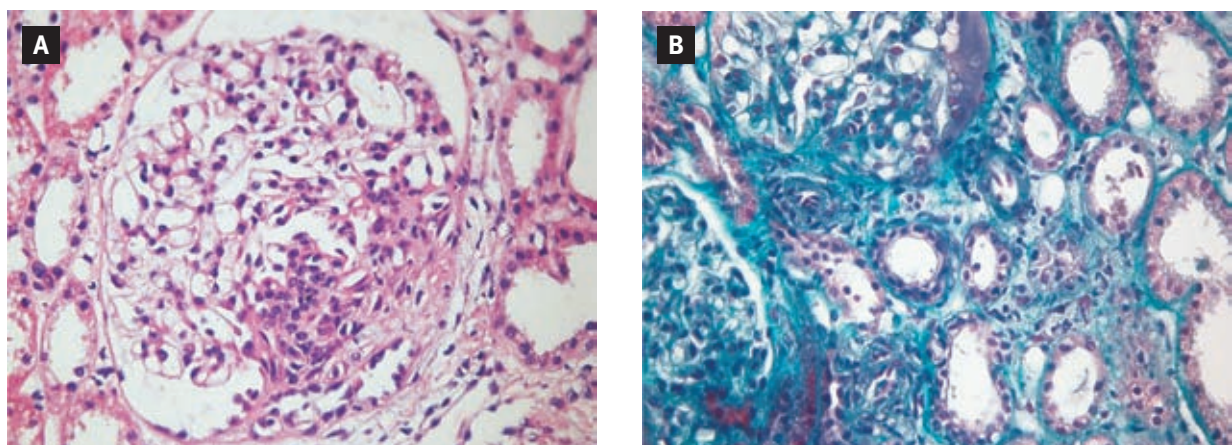


Figure 1

Diffuse proliferative glomerulonephritis with active lesions:

- a) Epithelial crescent (H&E x400)
- b) Segmental necrotising lesions (TM x400)

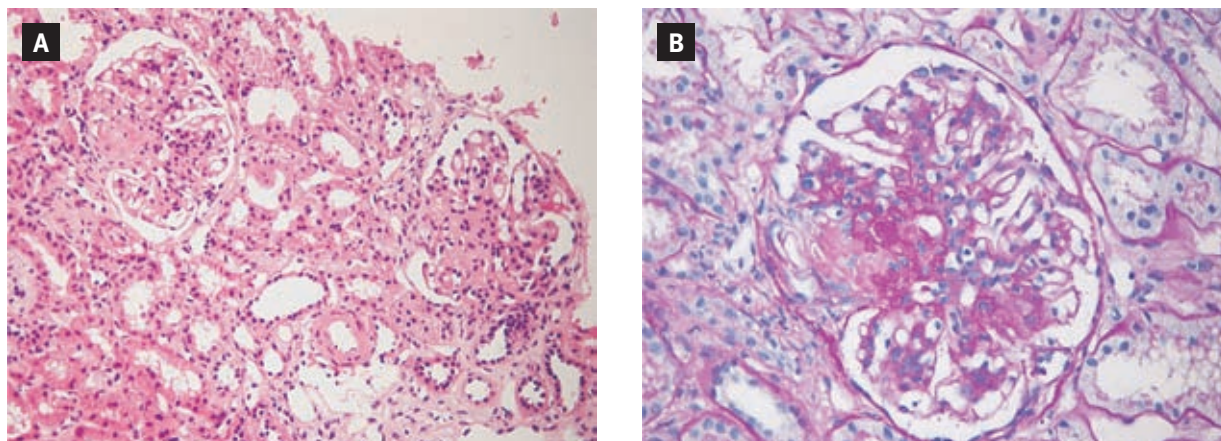


Figure 2

- a) Diffuse proliferative glomerulonephritis with active and chronic lesions (H&E x 400)
 b) Segmental glomerulosclerosis (PAS x400)

immunomodulating therapy, combined with MMF 1 g/day and corticosteroids in decreasing dosage (from 1.5 to 0.5 mg/kg/day), the patient showed significant clinical and immunological improvement. Disease activity decreased, including a fall in proteinuria to the lowest level since diagnosis (1.3 g/24 h) and partial recovery of renal function (serum creatinine level 1.9 mg/dl, corresponding to a glomerular filtration rate [GFR] using the MDRD formula⁴ of 34.5 ml/min/1.73 m²).

However, there was a clinical and serological deterioration before the 12th IV IG cycle, due to lupus reactivation with nephrotic syndrome aggravation, marked CKD deterioration (elevation of serum creatinine level to 4 mg/dl) and leucopenia. The patient completed this IV IG cycle (although in a lower dose, adjusted for renal function, of 15g IV for 4 days), combined with IV methylprednisolone pulses (1g for 3 days) with no clinical and/or laboratory improvement. Since this was a case of SLE with LN refractory to conventional immunosuppression instituted during the 46-month course of the disease, it was decided to administer rituximab IV (100 mg/m² of body surface area, 1 x week, 4 times) as a last resort. After the first and only cycle of this anti-CD20 monoclonal antibody, the development of severe leucopenia, thanks to a marked B-lymphocyte depletion, led to this treatment being stopped.

After 4 years of disease evolution, LN progressed to ESRD (GFR 14.6 ml/min/1.73 m²), with a residual diuresis of 1300 ml/day. Among the chronic renal replacement therapies presented, the patient chose peritoneal dialysis (PD) and a Tenckhoff catheter was introduced. After 17 days, she started a continuous ambulatory peritoneal dialysis (CAPD) programme on an initial prescription of 4 changes a day. As immunosuppression treatment, the patient was maintained only on corticosteroids in decreasing doses (from 0.5 to 0.1 mg/kg/day). After the first PD month, the peritoneal membrane function was assessed and already showed initial medium-high peritoneal transport (peritoneal equilibration test with a dialysate/plasma creatinine ratio = 0.72 at 4 hours) and adequate solute removal (Total Kt/V = 1.98 and creatinine clearance = 198 L/1.73 m²/wk), according to European⁵ and international⁶ guidelines. At the following monthly appointments, a rapid and marked fall in residual renal function (reduction of daily diuresis from 1,300 ml to 300 ml) was observed, despite diuretic therapy. There was also a progressive failure of the ultrafiltration capacity and the patient developed signs and symptoms of volume overload. After 4 months in PD, it was decided to construct a vascular access for haemodialysis (HD) – left humerocephalic arteriovenous fistula (AVF). During this period the patient had always presented significant hypoalbuminaemia (2.7-3.3 g/dl) in relation to nephrotic

proteinuria (5-8.5 g/24h), and serological tests indicated active lupus disease.h) and serological tests suggestive of active lupus disease.

Despite the constant adjustment of the dialysis prescription to ensure adequate solute and fluid removal by CAPD, in the 5th month of PD the patient developed acute uraemic pericarditis, accompanied by serious systolic and diastolic hypertension. The patient was then switched from peritoneal dialysis to HD (6 sessions a week, without per-dialytic anticoagulation), with non-steroid anti-inflammatory drug administration and optimisation of anti-hypertensive therapy. However, the second left humerocephalic AVF puncture was complicated by a large haematoma, requiring interruption of HD. The patient was temporarily transferred to continuous cyclic automatic peritoneal dialysis (APD-CCPD) for 2 days for AVF rest. Laboratory tests showed that this clinical situation was accompanied by pancytopenia associated with elevated anti-ds-DNA antibody count and deterioration of hypocomplementaemia. Since we could not exclude the possibility that lupus disease reactivation could have contributed, at least in part, to the onset of pericarditis, the corticoid therapy dose was increased (0.5 mg/kg/day) and a new IV IG cycle at 15 g for 4 days was instituted. With the medical and dialysis treatment, the patient showed significant clinical improvement and favourable echocardiographic evolution, with an approximately 6 kg reduction in body weight, blood pressure control and disappearance of the pericardial effusion. After recovery of leucopenia, corticoid therapy was combined with mycophenolate mofetil 500 mg b.i.d in an attempted to suppress lupus activity while on HD.

She was then included on a regular chronic haemodiafiltration (HDF) programme 4 times a week, with the following prescription: dialysate flow rate of 523 ml/min, blood flow of 350 ml/min and predilution replacement fluid infusion. After 4 months under HDF, extrarenal SLE manifestations reappeared: haematological (anaemia refractory to erythropoiesis-stimulating therapy, requiring several RBC transfusions, and leucopenia), ophthalmological (optic neuritis), and musculoskeletal (arthritis) complications, which required an increase in corticoid therapy to 1 mg/kg/day combined with MMF (1.5 g/day). Despite the patient's good compliance with dialysis, she had an excessive inter-dialysis weight gain associated with increased appetite and null

residual diuresis. At last, after 5 months under HDF, problems with the vascular access appeared; thrombosis of left humerocephalic AVF, right humerocephalic AVF, left humeroaxillary PTFE. The last one underwent thrombectomy with rethrombosis after 2 days, although no predisposing factors were identified (absence of circulating antiphospholipid antibodies and central venous stenosis on phlebographic examination related to a strong history of central venous catheters). Vascular surgery assessment considered the patient to be at increased risk of further peripheral vascular access thrombotic events, leading to a rapid loss of vascular resources.

In a period of better immunological stability, the patient was referred to transplant evaluation for live-donor transplantation. However, the cross-match with both parents was positive and so the patient remained on the active list for kidney transplantation from deceased donor. After 14 months under HDF (vascular access with tunnelised catheter at the right internal jugular vein allowing a mean blood flow rate of 200 ml/min), she was attributed a super-urgent status on the kidney transplant waiting list for imminent failure of vascular access and absence of PD conditions. After waiting for 4 months, she underwent desensitising treatment with IV IG (2 g/kg). The patient was submitted to cadaveric kidney transplant 10 days after the first cycle (HLA matches: A-1, B-0, DR-0) under quadruple induction immunosuppression with anti-CD25 monoclonal antibody (basiliximab IV 20 mg); mycophenolate mofetil (2 g/day), tacrolimus (0.1 mg/kg/day) and corticosteroids. As the patient's pre-transplant immunological study was positive for anti-cardiolipin antibody (IgM), she started oral anticoagulation with warfarin on day 10 after transplantation. The post-operative period was uneventful, with immediate diuresis, progressive reduction of nitrogen retention and serum creatinine level on discharge of 1.6 mg/dl. Serum creatinine levels after 1 and 2 months were 1.3 and 1.2 mg/dl, respectively.

■ DISCUSSION

SLE is a chronic, occasionally life-threatening, multisystemic disorder. The presence of kidney disease is the most important predictor of morbidity and mortality of SLE⁷, as illustrated in the case presented here. The aggressive course of the disease

described in our patient can be also correlated with the presence of other poor prognostic factors⁸, including low socioeconomic status, high number of American College of Rheumatology criteria for SLE, presence of hypertension, and high overall disease activity with persistent low complement.

Renal involvement occurs early in the course of SLE in about 25% of the patients and is largely mediated by deposit of immune complexes in the kidneys⁹. The optimal treatment of LN is uncertain given the relative scarcity of randomised controlled trials, but it varies with the type and the severity of disease present, as distinctive histological classes exhibit separate natural histories and clinical features¹⁰. The kidney biopsy performed in our patient, in the presence of relative mild renal manifestations (haematoproteinuria), revealed a diffuse proliferative glomerulonephritis, associated with an unfavourable prognosis in terms of both progression to ESRD and survival. Although it still carries the worst renal prognosis in most series, there is a gratifying response to early aggressive immunosuppression treatment with a cytotoxic agent in the majority of patients with active proliferative LN⁷. Unfortunately in our patient, and despite the optimal CYC treatment instituted (6 monthly infusions at a standard dose of 0.75 g/m² of body surface area, followed by pulses every third month for at least one year after remission), LN presented a severe frequent relapsing course during the first year of maintenance therapy, requiring extensive use of corticosteroids and alternative treatments, ultimately resulting in a progressive decline in renal function. The clinical risk factors for progression present in this case include: 1) early development of nephritis after SLE diagnosis, which is associated with a lower likelihood of sustained remission; 2) lack of response to CYC therapy with partial remission predicting a much higher probability of subsequent relapse compared to a complete remission; 3) early relapses after CYC therapy that generally do poorly; 4) relapses of active nephritis, with nephritic flares associated with an acute elevation in the serum creatinine holding an even greater risk of progression; 5) nephrotic-range proteinuria; 6) and finally, hypertension and anaemia^{11,12}. The crescent formation and the severity of tubulointerstitial disease also correlate with long-term prognosis in LN, as they do in other progressive glomerular diseases¹².

The optimal approach to severe relapses while on maintenance immunosuppression is not known. There are no established guidelines and the topic is open to active research. The relapse rate for LN has ranged from 35% to almost 60% of cases¹³. The present case is particularly interesting and infrequent as the patient became non-responsive to conventional immunosuppressive maintenance treatment: IV CYC, corticosteroids, MMF and ciclosporin. After the first flare, continuing the CYC quarterly treatment in a higher dose (maximum 1 g/m² of body surface area) was not an option, not only because of the development of impaired renal function, but also considering the risk of toxicity related to a cumulative dose of 10g (200 mg/Kg), particularly in terms of gonadal dysfunction and long-term malignancy. Alternative treatments were needed to treat this resistant form of severe active proliferative LN identified in repeated renal biopsy, using multiple concurrent agents.

The aim of modern therapy is to regulate rather than suppress the immune response. First, immunomodulation was tried with the adjunct therapy of high-dose IV IG plus MMF and corticosteroids. Several studies have analysed the benefit of IV IG in lupus nephritis¹⁴. Although the mechanism of action is not known, its immunomodulative effect is thought to be related to the: 1) modulation of macrophage-T cell function through a reversible Fc receptor blockade on effector cells, which leads to the inhibition of autoantibody synthesis of B lymphocytes; 2) enhancement of suppressor T cell function, which down-regulates autoantibody production; 3) manipulation of the anti-idiotypic network by direct neutralisation of pathogenic autoantibodies through idiotypic determinants and the formation of insoluble immune complexes, followed by removal via the reticuloendothelial system; 4) solubilisation and dissociation of glomerular IgG deposits, probably digested through anti-idiotypic antibodies¹⁵. The results were encouraging for almost a year on IV IG therapy free of relapses. In fact, an overall decrease of disease activity was seen, leading to improvement in the clinical (symptom amelioration, fewer hospital admissions motivated by complications, less absence from work with better quality of life), laboratory (proteinuria fell markedly to the lowest sub-nephrotic range and partial recovery of renal function) and immunological (complement increase) features. The toxicity was minimal and the most significant

disadvantage of IV IG therapy was its high cost. In addition, IV IG had an important steroid-sparing effect in that period, allowing a minimisation of the side-effects related to its prolonged use. We also think that from a more practical standpoint the IV IG therapy may have been useful in preventing serious infections in this patient whose immunodeficiency was due to both nephrotic syndrome and prolonged use of steroids¹⁶.

However, after a long period of clinical and immunological stability on IV IG plus MMF and corticosteroids, a new relapse of active nephritis occurred. Rituximab, a monoclonal antibody directed against CD20 B cells currently used for the immunotherapy of malignant lymphoproliferative disorders, has proved to be useful in inducing remissions in some patients with severe lupus nephritis non-responsive to standard immunosuppression¹⁷. The drug was added to the therapy as last resort. But the effects of immunosuppression outweighed the potential benefits, and the adjunct treatment was stopped. In fact, the disease process, in conjunction with the effects of long-term drug therapy, is known to cause significant morbidity, including frequent hospitalisations, increased susceptibility to infections and increased risk of cardiovascular disease, leading to the decision to stop rescue treatment.

The renal prognosis of LN has improved considerably over the years: no more than 10% to 15% of lupus patients develop ESRD within 8-10 years and lupus accounts for only 1% to 2% of all patients with ESRD¹³. Although every effort was made in treating this severe, frequently relapsing and resistant form of LN, the progression to stage 5 of chronic kidney disease was inevitable with scarring of the glomeruli after 4 years of therapy. The development of renal failure is, in most patients, associated with inactive “burn out” disease, with gradual or complete resolution of the extrarenal and serologic manifestations of lupus during the first year¹. The pathophysiology of this quiescence remains unclear. However, even during dialysis, SLE is still a variable disease. And, once more, in our patient the course was different, maintaining active disease with moderate to severe extrarenal symptoms (anaemia, leucopenia, arthralgias, pericarditis and optic neuritis) requiring vigorous treatment while on renal replacement therapy: MMF, corticosteroids, both in high dose, as well as IV IG. Treating this rare sub-

group of patients is difficult and the prognosis is serious, exposing uraemic patients to increased risk of infection and atherogenesis. They tend to have a poor nutritional state, lower serum albumin, lower body mass index and higher C-reactive protein values, all associated with poor prognosis in ESRD patients¹⁸.

The indications and the choice of renal replacement therapy for lupus patients are similar to those for other uraemic patients¹. Patient survival appears to be similar to that in the general population of patients with ESRD^{1,19}. However, SLE patients with ESRD may be at a higher risk of dialysis complications. In fact, there is an increased risk of death during the first months of dialysis, due primarily to sepsis and other complications of high-dose steroid therapy¹⁹. Later, infection, cerebrovascular and cardiovascular complications due to accelerated atherosclerosis (particularly premature myocardial ischemia) are common causes of morbidity and mortality on dialysis¹.

The prognosis of SLE patients on dialysis mainly depends on the general condition of the patient and disease activity at start. There are no differences in disease activity during either HD or PD, with comparable patient survival, although there is little information on the outcome in patients treated with PD^{1,19,20}. In line with patient preference and lifestyle, continuous ambulatory peritoneal dialysis (CAPD) was started. Nevertheless, the high activity of lupus disease during PD treatment, associated with a persistent systemic inflammatory status, damaged the peritoneal membrane leading to high-average transport from the outset and rapidly progressive type I ultrafiltration failure, with severe hypervolaemic symptoms. Therefore, transferral to continuous cyclic automatic peritoneal dialysis (APD-CCPD) was ultimately decided in an attempt to minimise ultrafiltration problems while waiting for reestablishment of HD vascular access. Actually, in SLE patients receiving PD, a poorer technique survival has been documented than in non-SLE PD patients, related to lupus activity, steroid treatment, higher peritonitis rate and lower predialysis serum albumin levels²¹. Moreover, a poorer prognosis in ESRD patients has been reported in SLE patients undergoing PD, in association with a 5-fold increase in all cause mortality, mostly due to infection and cardiovascular events²². It has also been suggested that SLE, which

can cause immune-mediated serositis, may be an additional factor predisposing to sclerosing encapsulating peritonitis development, a severe PD complication encumbered by elevated mortality²³. Therefore, and from what we learned from our own experience, it could be advisable to limit the PD indications to those patients with inactive SLE, who do not require corticosteroids.

The switch to HD was advisable and needed. The hypothesis that disease activity can be subdued by the removal of immune-complexes through the phagocytic systems in the lung during HD has been supported by numerous authors¹. In addition, experimental and preliminary human evidence suggests that large volume HDF using more porous membranes than conventional HD more effectively removes middle and large molecules with immunomodulatory properties²⁴. Nevertheless, our patient maintained a high disease activity with extrarenal SLE manifestations while on HD/HDF, requiring stepped up immunosuppression treatment. In fact and as previously noted, no benefits in terms of SLE activity and patient or technique survival have been documented in SLE patients treated with HD/HDF compared with PD. On the other hand, most patients demonstrate good tolerance to HD/HDF, until problems with vascular access appear. Although no antiphospholipid antibodies were initially found in our patient, there was a recurrent loss of all vascular access leading to a rapid depauperation of vascular resources.

As renal transplantation is considered the best therapy for most of the lupus patients with ESRD^{1,25}, particularly living donor transplant, a pre-transplant study was started after 6 months on HDF. However, the cross-match to living transplantation was positive for both parents. In fact, cross-matching negative donors may be difficult to find because the sera may contain antilymphocyte autoantibodies, rendering a false-positive result. This can lead to a long waiting period on the deceased donor transplant list, even with the super-urgent status, and a successful desensitising treatment was the next step. IV IG was used again, in a higher dose, as it has been demonstrated to be a potent inhibitor of anti-HLA antibodies and to permit transplantation with minimal risk of rejection²⁶. The transplant was performed after 4 months waiting on deceased donor list with super-urgent status, and special care was

taken in choosing quadruple immunosuppression and prophylactic oral anticoagulation shortly after surgery, with excellent results.

Yet, the fact is that this was a particularly aggressive SLE case in a young patient with a hectic activity, raising new and worrying questions for the future: although the first two post transplant months have been free of complications, what is going to be the course of this SLE recipient and graft survival? And the clinical challenge still remains...

Conflict of interest statement. None declared.

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