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CASE REPORT

Successful renal transplantation in a patient with a Wiskott–Aldrich syndrome protein (*WASP*) gene mutation

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Summary

Wiskott–Aldrich syndrome (WAS) is a rare primary immunodeficiency disorder caused by mutations in the WAS protein (*WASP*) gene. Renal disease progressing to renal failure is a well-recognized complication in patients with WAS. Only a few case reports of renal transplantation have been reported to date. Here, we present a patient with a *WASP* mutation who suffered from severe atopic eczema, mild thrombocytopenia and only a slightly increased frequency of infections, who then developed IgA nephropathy and consequently underwent renal transplantation, which was successful. This study demonstrates that renal transplantation is possible in patients with WAS, regardless of conceivable complications.

Introduction

Wiskott–Aldrich syndrome (WAS) is a rare, X-linked primary immunodeficiency disorder [1] caused by mutations in the WAS protein (*WASP*) gene [2]. The WAS protein is exclusively expressed in haematopoietic cells and is a key regulator of actin polymerization [3,4].

The clinical manifestations in patients with *WASP* mutations are highly variable and depend on the type of gene mutation [5]. The majority of patients suffer from classical WAS, characterized by a triad of small-platelet thrombocytopenia with bleeding tendency, recurrent infections and severe eczema, with an increased risk of autoimmune disorders and lymphoid malignancies. Patients with X-linked thrombocytopenia, a milder variant of WAS, suffer predominantly from thrombocytopenia [6]. If not treated with haematopoietic stem cell transplantation (HSCT) in infancy or childhood, patients with WAS die of intracerebral bleeding, severe infections or lymphoma. Only in a minority of cases with a mild clinical course do patients survive into adulthood without HSCT.

Autoimmune diseases are frequent complications in patients with WAS, the most common being autoimmune haemolytic anaemia [7,8]. Renal disease, a common complication in WASP deficiency, is observed in 3.5–19.0% of all cases [8,9] and includes membranoproliferative glomerulonephritis, interstitial nephritis and IgA nephropathy (IgAN) [10,11]. All of these renal diseases may progress to chronic renal failure requiring renal transplantation, which may be difficult and disfavoured by transplant surgeons due to established immunodeficiency in patients with WAS. Therefore, only a few cases of kidney transplantation

have been reported in the literature [12–14] with low success rates.

Here, we report a patient with a *WASP* mutation who suffered from severe atopic eczema and mild thrombocytopenia without bleeding tendency and only a mildly increased occurrence of infections who developed IgAN and consequently underwent renal transplantation, which was successful.

Case report

The patient was referred for immunological investigation at the age of 16 years because of severe eczema that began in his first month of life and an incidental finding of thrombocytopenia with small platelets (Table 1). He suffered from a slightly increased frequency of mild, recurrent respiratory tract infections without severe or life-threatening complications. The immunological investigation revealed the typical picture of patients with WAS (Table 1). Mutation analysis of *WASP* showed a splice site mutation (3′ intron + 4, CTC to CCC) in exon 11, which was highly likely to be disease-causing. Subsequent Western blot analysis revealed residual expression of *WASP*.

At 17 years, mild haematuria and proteinuria were observed. A renal biopsy performed at 21 years showed IgAN, but no treatment was necessary. However, at 26 years, the patient developed end-stage renal failure [urea: 18.3 mmol/l and serum creatinine (SCr): 349 μmol/l] with anaemia and hypertension. Intravenous immunoglobulin (IVIG) replacement (250 mg/kg/month) was initiated at 27 years, even though the patient did not suffer from a markedly increased frequency of infections. Haemodialysis was also initiated.

Eight months after haemodialysis was initiated, the patient underwent kidney transplantation from a deceased donor. There was only one mismatch in the B locus (donor: B13, 14 and recipient: B13, 62); no special induction therapy was used. The patient's primary immunosuppression regimen consisted of mycophenolate mofetil (1.0 g/day), tapering to 0.5 g/day on day +60; 10 mg/kg of cyclosporine A (CyA), tapering to a target 2-h postdose (C2) concentration of 1300 ng/ml ±20% for 1–3 months, 1100 ng/ml ±20% for 4–6 months and 900 ng/ml ±20% for 6–7 months after transplantation; and intravenous methylprednisolone doses of 500, 250, 125 and 40 mg on days 1, 2, 3 and 4, respectively, followed by 30 mg of prednisone on day 5, decreasing to 5 mg/day on day +90. Because the patient developed

Table 1. Typical laboratory findings in patients with Wiskott–Aldrich syndrome and laboratory findings in the current patient.

Laboratory investigation (reference ranges)	Typical laboratory findings in patients with WAS	At the time of diagnosis (16 years)	At the time of CRF biopsy-confirmed IgAN (26 years)	1 month before RT (27 years)	3 years a fter RT (good graft function)	6.5 years after RT (recurrence of IgAN)	3 years after GF waiting for the second RT
IgG (7.51–15.60 g/l)	Within a normal range	10.6	9.0	9.12*	10.90*	7.16*	12.00*
IgA (0.82–4.53 g/l)	Increased	6.4	10.30	6.56	10.30	6.79	6.19
IgM (0.46–3.04 g/l)	Decreased	0.28	0.18	0.10	0.16	0.14	0.18
IgE (0–100 IU/ml)	Increased	644	2660	n.d.	1190	1210	594
$CD3^+$ (0.90–2.80 × 10^9 l)	NA	0.90	0.66	1.00	4.02	1.01	0.96
$CD3^+CD4^+$ (0.40–1.40 × 10^9 l)	NA	n.d.	0.49	0.77	1.07	0.59	0.39
$CD3^+CD8^+$ (0.20–0.90 × 10^9 l)	NA	n.d.	0.15	0.22	2.78	0.32	0.48
$CD19^+$ (0.1–0.5 × 10^9 l)	NA	n.d.	0.15	0.16	0.13	n.d.	0.07
$CD16^+/56^+$ (0.09–0.60 × 10^9 l)	NA	n.d.	0.38	0.39	0.13	n.d.	0.10
IgG anti-TET (>0.120 IU/ml)	NA	0.170†	0.115†	0.100†	n.d.	n.d.	n.d.
IgG anti-PPS (>15.4 mg/l)	NA	16.5†	99.3†	87.2†	n.d.	n.d.	n.d.
IgG anti-HIB (0.09–17.7 mg/l)	NA	0.013†	0.703†	0.182†	n.d.	n.d.	n.d.
PLT (150–400 × 10^9/l)	Decreased	34	30	50	82	49	51
MPV (7.80–11.00 fl)	Decreased	6.5	7.9	8.80	8.50	8.20	8.20
Urea (1.70–8.30 mmol/l)	NA	5.4	18.3	9.00	9.40	22.20	20.40
Serum creatinine (44–115 μmol/l)	NA	72	349	434	109	309	728

$CD3^+$, T lymphocytes; $CD3^+CD4^+$, helper and regulatory T lymphocytes; $CD3^+CD8^+$, cytotoxic T lymphocytes; $CD19^+$, B lymphocytes; $CD16^+/56^+$, NK cells; anti-TET, antibodies against tetanus toxoid; anti-PPS, antibodies against pneumococcal polysaccharides; anti-HIB, antibodies against *Haemophilus influenzae type b*; PLT, platelets; MPV, mean platelet volume; GFR, glomerular filtration rate; IVIG, intravenous immunoglobulin; CRF, chronic renal failure; RT, renal transplantation; WAS, Wiskott–Aldrich syndrome; IgAN, IgA nephropathy; GF, graft failure; NA, not applicable; n.d., not determined.

*The patient was on IVIG treatment at a dose of 250 mg/kg/month.

†The patient was vaccinated only against tetanus toxoid within regular immunization schedule in the Czech Republic.

cyclosporine gingival hyperplasia 7 months after transplantation, CyA was switched to tacrolimus, with a target level of 4–6 μg/l. The postoperative course was uncomplicated with good graft function; at discharge on day 28, the patient's SCr level was 148 μmol/l and the glomerular filtration rate (GFR) was 0.940 ml/s. Despite normal clinical practice in immunocompetent patients, the administration of prednisone was terminated 18 months after transplantation. At that time, the patient had stable renal function (SCr 114 μmol/l, GFR 1.450 ml/s).

In the subsequent post-transplantation period, the patient continued with IVIG treatment (250 mg/kg/month) and his atopic eczema markedly improved, although chronic lichenification persisted. During this stable period, his immunosuppression regime consisted of tacrolimus and mycophenolate mofetil. He did not suffer from an increased frequency of respiratory tract infections; facial herpes zoster at the age of 32 was successfully treated with oral acyclovir. Also at 32 years of age, warm-type autoimmune haemolytic anaemia was successfully treated with methylprednisolone therapy, tapering from a dose of 32 mg to 4 mg by stepping down the dose every 2 days. This 6.5-year-long post-transplantation period was uneventful, enabling the patient to work at a part-time job.

At the age of 35, the patient suffered from oedema of his lower extremities. A graft biopsy showed a relapse of IgAN (treated by 250 mg pulse dosing intravenous methylprednisolone for 3 days followed by increase in oral methylprednisolone to 16 mg/day for 2 weeks without clinical effect). A rapid decrease in graft function over 3 months led to reinitiation of the haemodialysis programme 6.5 years after transplantation. One year later, the patient was hospitalized in the neurosurgery department for an otogenic brain abscess caused by *Pseudomonas aeruginosa*. His condition was successfully treated with stereotactic puncture and cefotaxime with metronidazole. This therapy led to complete interruption of the immunosuppressive treatment.

At the time that this case report was completed, 10 years had elapsed since the first transplantation. The patient was 38 years of age, was in a relatively stable state, did not have significant immunodeficiency symptoms and was waiting for a second suitable donor.

Discussion

Several renal diseases may lead to renal failure in patients with WAS; IgA nephropathy has been diagnosed in a majority of these cases [15]. In addition to our case, 10 cases of WAS/X-linked thrombocytopenia (XLT) with biopsy-confirmed nephropathy were previously described [10]. To our knowledge, we describe the first case of successful renal transplantation without serious complications over 6.5 years of good kidney graft function in a patient with a *WASp* mutation and biopsy-proven IgAN.

Renal transplantation is complex in patients with WAS due to the underlying immunodeficiency and the increased risk of lymphoma [12]. Therefore, only a few cases of renal transplantation have been reported (Table 2). The first three reported transplantations were performed in the 1990s, when the standard triple-therapy protocol used for transplantation consisted of azathioprine (2.0 mg/kg), CyA (5.0 mg/kg) and prednisone (0.5 mg/kg) [16]. The immunosuppressive treatment in patients described by Webb *et al.* [14] and Meisels *et al.* [13] was reduced in comparison with that used in immunocompetent patients, but Fischer *et al.* [12] used standard doses of this triple immunosuppressive therapy. The higher, standard doses could be the reason for the fatal outcome in the latter patient, who had complications from multiple infections and lymphoid malignancy 3 months after transplantation (Table 2).

Table 2. Three previously reported cases of renal transplantation in patients with WAS.

			Immunosuppression				
Patient	Biopsy	Type of RT	AZA	CyA	MPD	Outcome	References
46-year-old man	MesPGN	One haplotype matched; deceased donor	1.0 mg/kg	5.0 mg/kg (C0: 100–150 ng/ml)	0.5 mg/kg	No rejection; death 35 months after RT (probable cardiac cause)	[14]
33-year-old man	MPGN	Deceased donor	1.0 mg/kg	8.0 mg/kg (C0: 250–375 ng/ml)	0.3 mg/kg	BPCR on day 26 after RT	[13]
41-year-old man	n.d. (brother IgAN)	One Haplotype matched; living related donor	2.0 mg/kg	(C0: 200–250 ng/ml)	0.5 mg/kg	BPCR on day 76 after RT; multiple infectious complications and lymphoid malignancy; death 3 months after RT	[12]

AZA, azathioprine; CyA, cyclosporine A; MPD, methylprednisolone; MesPGN, mesangioproliferative glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; C0, trough level; BPCR, biopsy-proven cellular rejection; RT, renal transplantation; n.d., not determined.

Because azathioprine was replaced with mycophenolate mofetil in combination with CyA or tacrolimus and prednisone as the standard protocol at the end of the 1990s [17,18], our patient was treated with a standard dose of mycophenolate mofetil, prednisone and CyA, which was switched to a standard dose of tacrolimus. In our patient, steroid therapy was interrupted 18 months after transplantation to decrease the risk of infectious complications.

Patients with WAS/XLT were recently shown to produce aberrant galactose-deficient IgA, which can participate in development of IgAN [19]. Furthermore, HSCT ameliorated IgAN and causes decrease in aberrant IgA in the serum of patient with WAS [20]. Nevertheless, HSCT was not indicated in our patient because of mild clinical course of the disease.

Unlike our case, all three previously reported WAS transplant patients had strong family histories of WAS disease, and the clinical features typical for these patients were well expressed. Although he has a *WASP* mutation, our patient likely suffers from a mild clinical form of WAS, particularly regarding infectious complications, which could explain his uneventful post-transplant period.

In conclusion, our case of successful renal transplantation reinforces the fact that renal transplantation is possible in patients with WAS, especially those with a milder clinical form of the disease, regardless of possible complications. These patients may tolerate appropriately reduced chronic immunosuppressive treatment.

Authorship

ZC: collected the data and wrote the paper. MK: contributed clinical data. MV: contributed laboratory data. JL: supervised the evaluation and interpretation of data and clinical information.

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