De-Novo IgA Nephropathy and Cyclosporine Toxicity After Heart Transplantation

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Introduction

IgA nephropathy (IgAN) is the most common type of glomerulonephritis (GN) accounting for about 15%–20% of all GNs in Europe and 30%–40% in Japan but is less often observed in North-America (1,2). The diagnostic hallmark of IgAN is mesangial deposition of immunoglobulin A (IgA) often together with complement-3 (C3) in the glomeruli and some patients with IgAN may have increased levels of circulating immuno-complexes containing IgA. IgAN, initially considered to be a disease with benign prognosis, may eventually progress to end-stage-renal disease (ESRD) in 15%–40% of the cases (2,3,4). In order to predict outcome in patients with IgAN a grading of glomerular changes from kidney biopsies has been used (5). The etiology of IgAN is still not known but several observations point to some involvement of ethnic and genetic factors (6,7).

Acute myocarditis (AM) accompanied with acute heart failure may need intensive care treatment and with a progressive course an early heart transplantation (HTx) might be offered if a suitable heart-donor is present. Different kinds of viruses may often cause AM and Coxsackie B-virus, Cytomegalovirus, Adenovirus, and Influenza A-virus, are accounting for most of the cases.

End-stage renal failure (ESRF) is a well known late complication of HTx (8) with a poorer outcome than in other ESRF (9) subjects. ESRF may be related to hypertension regardless of their immunosuppressive regimen (9,10), or related to different infections, including sepsis, and to their treatments (9,10). However, calcineurin inhibitor nephrotoxicity (CIN) is the most recognized late renal complication after HTx (10,11). Different forms of *de-novo* GNs like membranous, membranoproliferative GN, and IgAN have been reported after solid organ transplantation (12,13). Immune-complex deposit glomerulopathy (15), and focal segmental glomerulosclerosis have been observed after HTx (10,14).

Our case had acute myocarditis with rapid progressive heart failure needing a heart transplantation. Subsequently chronic renal failure developed and a kidney biopsy performed seven years after HTx confirmed global glomerular sclerosis and IgA nephropathy.

Case

A previously healthy man, 31 years-of-age, was admitted to our hospital due to abdominal cramps, vomiting, diarrhea, and suspicion of gastroenteritis. Three days before he had been prescribed roxitromycin (Roxibion®, Schering-Plough Corp., Kenilworth, NJ, U.S.A.) and brompheniramine maleate (Dimetane®, Wyeth-Lederle, Madison, NJ, U.S.A.) by his doctor because of an acute respiratory infection. Pain of the joints was absent. His medical history included surgery of phimosis as a child, and 25 years ago he had conservative treatment for osteochondritis dissecans of the left femoral medial condyle. No episodes of macroscopic and/or microscopic haematuria had been observed earlier which was also absent during the military service.

His mother and his older sister died at the age of 50 years and 16 years, respectively, both due to systemic lupus erythematosus (SLE). His father, 80 years-of-age, is still healthy. His twin sister has microscopic haematuria which now is under examination.

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At arrival to our hospital his general condition was impaired, with drowsiness, bad looking skin color, in a cold sweat, and cold extremities. Systolic blood pressure (sBP) varied between 80 to 90 mmHg with temporarily even lower sBP and the diastolic pressure was not measurable. His heart-rate was 93 beats/min. The chest x-ray examination was normal. Electrocardiogram (EKG) showed sinus-tachycardia with non-specific ST elevation in precordial leads and otherwise without pathology.

Clinical examination of abdomen remained unremarkable. Abdominal ultrasound examination disclosed normal pancreas, spleen and kidneys, liver and biliary system, with some intra-abdominal fluid retention. Some selected laboratory tests taken at arrival and later are shown (Table 1). No pathogens, virus, bacteria, or other, could be found. A slight initial thrombocytopenia (101×10^9/L) was corrected within the next day. Number of leukocytes and serum C-reactive protein (s-CRP) concentration (0 mg/L) remained normal. All immunological tests for diseases like SLE (DNA-antibodies), rheumatoid arthritis (Rheumatic factor), anti-cytoplasmic nuclear antibodies, and tests for HIV, hepatitis C-virus, Cytomegalovirus, Epstein-Barr virus were negative. Serum complement C3 and C1 were low, 0.8 g/l (ref. value 0.9–1.8 g/l) and 0.1 g/l (ref. value 0.1–0.4 g/l), respectively. The 24 hour urine collection contained 119 mg of protein.

Echocardiography, performed shortly after arrival disclosed a left ventricular end diastolic diameter of 46 mm and end systolic diameter 44 mm. Ejection fraction was only 12%. Otherwise the heart structure was normal. These findings were supportive to the clinical diagnosis of acute myocarditis with myocardial failure. In order to stabilize his condition he was treated at the intensive care department during the next 24 hours whereafter he was forwarded to Helsinki university hospital for further treatment. Successful HTx was performed 20 days later.

Two months after HTx, when he was returned to our hospital for follow-up, the serum creatinine concentration (s-creat) was 89 μmol/l increasing to 109 μmol/L six months later and during the next years it continued to rise (Table 1). The increase in s-creat was assumed to be caused by cyclosporine-A (CyA) toxicity. During the years to follow examination for microscopic haematuria and proteinuria was occasionally performed and when

Table 1. Some selected laboratory results describing the development of renal failure after heart transplantation, prior to and after kidney biopsy, and at highest plasma creatinine level (max creat).

Type of laboratory	Before HTx Arrival/24 hrs	After HTx 2 mo	4 mo	6 mo	1 year	2 years	4 years	At max. creat.	Before biopsy	Today
Hgb (g/l)	139	138	133	132	124	121	128	118	126	111
CRP (mg/l)	0	0	0	0	0	0	0	0	0	0
P-Creat (μmol/l)	79	89	90	109	138	145	150	203	182	146
P-Urea (mmol/l)	4.1	NE	NE	NE	NE	NE	11	13	16	12
B-CyA (μg/l)	NE	438	296	206	208	179	125	223	119	95
Urine (erys +/–)	NE	NE	NE	0	NE	NE	0	0	+5/fov	17–2/fov

HTx: heart transplantation; hrs: hours; mo: months; NE: not examined; Hgb: haemoglobin concentration; CRP: C-reactive protein concentration; P-Creat: plasma creatinine concentration; P-Urea: plasma urea-nitrogen concentration; B-CyA: blood cyclosporine concentration; Urine: urine examination for erythrocytes; fov: field of vision.

microscopic haematuria was detected and s-creat had increased further to 203 μmol/ the nephrologist was consulted. In October 2007 a kidney biopsy was performed.

Kidney Biopsy

The kidney biopsy was adequate containing 27 glomeruli of which 17 (63%) showed extensive global sclerosis (Fig. 1). In the preserved glomeruli mild widening of the mesangium with increased matrix and hypercellularity was observed (Fig. 2). No double membranes, crescents or spikes were found. A mild interstitial atrophy was present. Blood vessels were normal with no signs of wall thickening. Thrombotic microangiopathy, interstitial fibrosis, tubular atrophy, tubular calcifications or vacuolization were not observed. According to the WHO grading the preserved glomeruli were grade IIB corresponding to mesangioproliferative GN and those globally sclerosed glomeruli grade V, chronic sclerosis.

Direct immunofluorescence examination of frozen sections disclosed strong co-dominant granular deposits of IgA and complement C3 in the mesangium. In addition, very weak staining for IgM, IgG, and fibrinogen was observed. Staining for IgA was also found at indirect immunohistochemical examination (Fig. 3).

Clinical Course

Beside three episodes of mild acute rejection, treated successfully with short-term high-dose corticosteroids, the clinical course of the heart transplant was uneventful. During the years after HTx he often, almost every year, suffered from some short periods of respiratory infections which was treated with antibiotics.

Following the evaluation of the kidney biopsy specimen and consistent with previous reports (15), in agreement with the cardiologist, it was decided to reduce the CyA dose and to add mycophenolate mofetil (MMF; CellCept®, Hoffman-La Roche, Basel, Switzerland) to the treatment regimen. As a consequence of this rearrangement the s-creat has remained stable. No further transplant rejections have been registered after change of treatment to CyA plus MMF.

Discussion

To our best knowledge, this is the second report on a subject developing *de-novo* IgA-N after orthotopic heart transplantation. The first case of IgAN and another case with immuno-complex deposit GN after orthotopic HTx were recently presented in a poster by Garcha et al. at the National Kidney Foundation (NKF) Spring Clinical Meeting in 2008 (13). Similarly to their, our patient also developed *de-novo* IgAN in spite of ongoing immunosuppressive treatment, pointing to other mechanisms to be involved in the development of IgAN than those suppressed by CyA and corticosteroids. In general, our observation together with the previous one (13) might explain why CyA treatment was found insufficient in the treatment of IgAN. While their patient with *de-novo* IgAN presented with nephrotic range

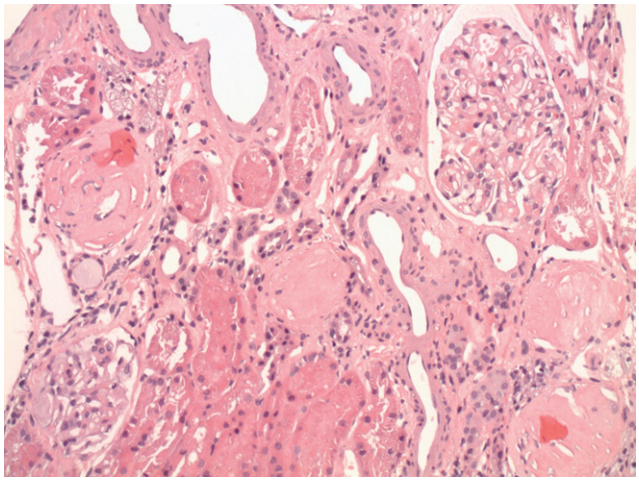

Figure 1. Several globally sclerosed glomeruli and two glomeruli with hypercellularity and mild widening of the mesangium by increased matrix (H&E stain, 200 x magnification).

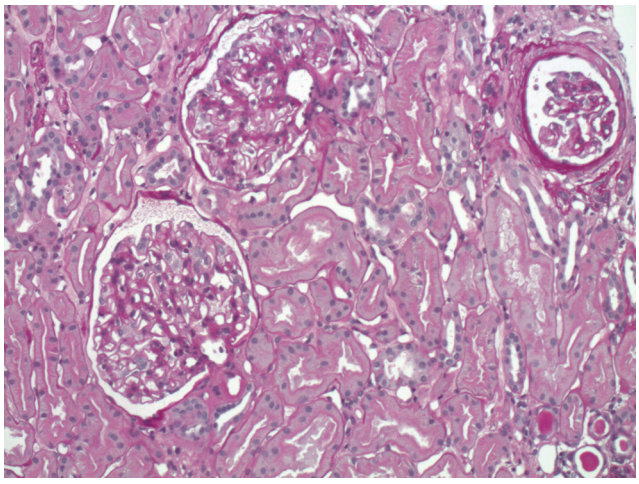

Figure 2. Mild glomerular hypercellularity and slight increase of mesangial matrix (PAS stain, 200 x magnification).

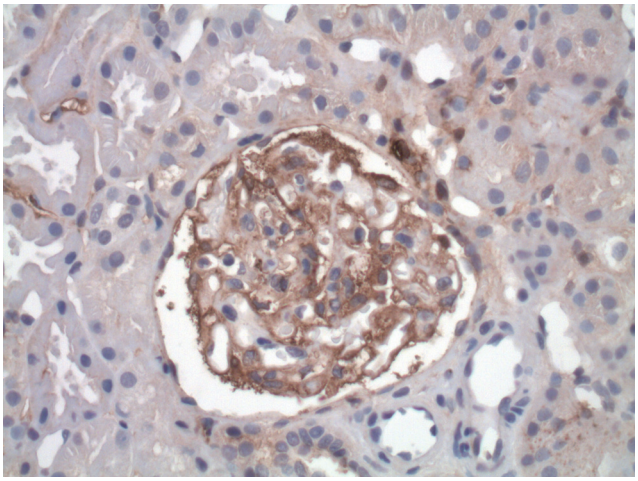

Figure 3. Strong staining of IgA in glomerular mesangial matrix (indirect immunohistochemical stain for IgA, 400 x magnification).

proteinuria which was absent in our case, our patient had sporadic episodes of microscopic haematuria. Heavy proteinuria is neither a common feature of IgAN nor in CyA nephrotoxicity, however. Treatment with corticosteroids, azathioprine and cyclophosphamide might eventually be of some benefit in patients with IgAN (16,17,18).

As macro and micro-hematuria was absent in his anamnesis, and during the military service over a decade ago, it seemed unlikely that the IgAN was present prior to the acute myocarditis as also not before the shortly thereafter performed HTx. Examinations of urine for microscopic hematuria were only occasionally performed, the reason why no conclusions can be made to whether the same agent, assumable a virus that caused myocarditis also initiated IgAN. However, in several urine examinations performed after HTx microscopic haematuria was not found, pointing to a later occurrence of the IgAN. In fact he had suffered from several short courses of mild respiratory infections almost every year after the HTx which may have initiated his IgAN. This, together with a possible familiar clustering (6,7) might be an explanation for the IgAN in our subject.

Viruses are important agents in the development of cardiac and renal diseases and circulating antibodies against Haemophilus parainfluenza have been reported to exist in sera from patients with IgA-N (19). Furthermore, both patients reported by Garcha et al. (13) also had virus-myocarditis. Thus, the virus infection might be the etiologic stimulator to both myocarditis and IgAN in their patient. Such an explanation seems less suitable in our case as no proteinuria or microscopic hematuria was present until late in the course of chronic renal failure.

Renal involvement in systemic lupus erythematosus (SLE) is a typical manifestation of the disease, and the co-existence of IgAN in patients with SLE has been reported (20,21). Although both his mother and sister suffered from SLE, our patient had no clinical signs of SLE and all laboratory tests related to SLE were negative. Still, one might speculate whether a possible link between SLE and IgAN in our patient did exist thereby having a genetic predisposition to develop IgAN in combination with the previous mentioned respiratory infections.

Some of the pathological findings in our kidney biopsy specimen may be linked to CyA toxicity and the glomerular changes were probably due to vasoconstriction with secondary global glomerular sclerosis, a feature often reported in CIN. These changes would explain the initial increase in s-creat about 6–12 months after HTx, and the decrease in s-creat after reducing the dose together when adding MMF to the treatment schedule. Moreover, IgAN may have developed much later as an isolated entity just being a co-incidence. IgAN is the most common biopsy-proven GN in the world, and therefore it is to believe that the IgAN occurred totally independent from HTx.

The mild interstitial atrophy and glomerular sclerosis may be partly related to CyA toxicity, but may also be overlapping features of IgA nephropathy. Arteriolar hyalinosis, microangiopathic changes, marked tubular atrophy or vacuolization were not observed in the biopsy. Renal infarction seemed not likely as the biopsy findings included both totally sclerosed and mildly hypercellular glomeruli intermixed with each other (Fig. 2). This is not typical for renal infarction in which all glomeruli in the biopsy usually are sclerosed. In addition, interstitial scarring should be prominent after infarction, also absent here.

Development of *de-novo* glomerulopathy has been observed other nonrenal solid organ transplanted subjects. Paller et al. (22) reported three patients which following lung transplantation developed nephrotic-range proteinuria 2 to 5 years post-transplantation and focal segmental glomerulosclerosis was found in two patients and probable focal sclerosis in eth third. Focal segmental glomerulosclerosis with collapsing variant probably associated to CyA toxicity have been

described (23). Biopsy proven IgAN with segmental crescents and progressive renal failure was reported after liver transplantation (24). In patients with chronic renal failure (CRF) after HTx the reason for CRF, as judged from biopsy materials, was almost always due to CIN. Ojo et al. (25) reported an increased numbers of CRF after liver, intestine, lung, and HTx. CRF was found in 16.5% of the transplanted subjects, and ESRD in 28.9% of those who had an earlier diagnosis of CRF. CRF developed at a rate of 1.0%–1.5% every year after transplantation (25). Some recovery of the renal function could eventually be achieved after switching to a lower dose of CyA and adding MM to the treatment regimen (26). CyA-free treatment and sirolimus was not used in our patient.

In conclusion, IgAN may develop in spite of the use of immunosuppressive treatment with CyA and corticosteroids, which point to other types of mechanism involved in its development. Respiratory infections might be of importance when IgAN (and maybe other GNs) occurs in non-renal solid organ transplanted subjects. Renal biopsy is essential in order to differentiate CyA toxicity from other types of GNs that may develop after HTx and should be performed even with low grade of renal failure. The presence of IgAN (and GN) may induce modification of the mode of immunosuppressive treatment in these subjects. In our case, the IgAN seemed to be a rare co-incidence.

Disclosure

The authors report no conflicts of interest.

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