JKBMS, Vol.4, No.2, P.43-47, 2018 https://doi.org/10.56056/amj.2018.58

Thrombotic Microangiopathy Complicating Cyclosporine in Renal Transplant Patients

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Abstract

Background and objectives: Experience with cyclosporine associated thrombotic microangiopathy in renal allograft recipients is generally anecdotal; detailed descriptions of clinical behavior, therapeutic options and experience are also anecdotal and few. The aim of this study was to identify possible contributing factors to cyclosporine associated thrombotic microangiopathy, and to investigate therapeutic modifications that result in better graft survival in these patients. **Methods:**One thousand and twenty patientstients evaluated for this study received live related or unrelated kidney transplants at Rizgary teaching hospital and Zheen international hospital between July 2011 and September 2016. The patients received standard induction therapy with anti-thymocyte globulin or basliximab and cyclosporine or mycophenplate and steroids. Regular follow up with blood film and counts, reticulocyte count, liver enzymes, renal function tests, lactic dehydrogenas, haptoglobin and serum electrolytes were performed. **Results:** The prevalence of cyclosporine associated thrombotic microangiopathy was 1.73%; of which 4(26.7%) were male while 11(73.3%) were female, with male to female ratio of 1:2.75. Mean age ±standard deviation of 36.87±10.927. Chronic glomerulonephritis was the most frequently distributed type of pre-transplant diagnosis 5 (33.3%), followed by focal segmental glomerulosclerosis 4 (26.7%) and diabetes mellitus 3 (20%). Live related was the maximum frequent 10 (67%) while live unrelated is the minimum frequent 5 (33%).**Conclusions:** Thrombotic microangiopathy is a well-known complication of cyclosporine. Paying attention to signs of hemolysis and thrombocytopenia in the blood film are important clues in detecting early the diagnosis.

Keywords: Cyclosporine associated thrombotic microangiopathy; Focal segmental glomerulosclerosis; Hawler teaching hospital- Kidney disease center.

Introduction

Since the advent of cyclosporine (CsA), thrombotic microangiopathy (TMA) has been observed as a side effect of this form of therapy in bone marrow graft recipients[1] and in patients treated with solid organ trans- plantation, including kidney[2–8]. The occurrence of TMA in patients receiving CsA for conditions not related to transplantation, such as uveitis[5], rheumatoid arthritis[8] and psoriasis[2] indicates a possible causal relationship between this drug and the microangiopathic process. It is noteworthy that only a minority of the patients with CsA-associated TMA has the full clinical picture of hemolytic uremic syndrome[9] and that the diagnosis is frequently not apparent before renal biopsy is performed.

Diagnostic histopathological changes in the acute phase of CsA-associated TMA have been described in detail in glomeruli and arterioles[10]. Fibrin thrombi, focal necrosis, and mesangiolysis of the glomerular tuft, sometimes accompanied by cellular crescents, are associated with occlusive concentric cellular proliferation of the arterioles, which also frequently show fibrin thrombi[3, 11]. Although vascular rejection generally affects muscular arteries, it is occasionally accompanied by fibrin thrombi in arterioles and glomerular capillaries[12]. The chronic changes of CsA-associated TMA include hyalinization of the arterioles, duplication of the glomerular basement membrane, segmental and global glomerular basement membrane, segmental and global glomerulosclerosis, interstitial fibrosis, and tubular atrophy[3, 10, 13-15].

Experience with CsA-associated TMA in renal allograft recipients is generally anecdotal. Detailed descriptions of clinical behavior, therapeutic options, and experience with CsA-associated TMA in renal allograft recipients is also anecdotal, and detailed descriptions of clinical behavior, therapeutic options, and outcomes are few[16]. The aim of this study was to identify the incidence of

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CsA-associated TMA, and to describe patients clinical and lab data associated with CsA-associated thrombotic microangiopathy.

Patients and methods

One thousand and twenty patients evaluated for this study received live related or unrelated kidney transplants at Rizgary teaching hospital and Zheen international hospital between July 2011 and September 2016. The CsA-associated TMA cases are diagnosed at the Hawler teaching hospital- Kidney disease center. The patients received standard induction therapy with either anti thymocyte globulin ATG or basliximab and cyclosporine, mycophenplate and steroids. Regular follow up with blood film and counts, reticulocyte count, liver enzymes, renal function tests, Lactate dehydrogenase LDH level and serum electrolytes were performed.

Thrombotic microangiopathy (TMA) was defined when hemolytic anemia, reticulocytosis, shistocyte count more than 5%, low haptoglobin HGL and high LDH level.

Inclusion criteria in the current study required the presence of microangiopathic hemolytic anemia (schistocyte count of more than 5%), low haptoglobin levels (normal value:30-200mg/dl), elevated reticulocyte count (more than 3% when corrected to the PCV), high serum LDH (normal value:140-280 U/L), impaired renal function (creatinine more than 1.5 mg /dl) and thrombocytopenia (platelet count below 100,000 per cubic millimeter or less than 50% percent of the initial count).

Kidney biopsy was not performed in the index patients because of the thrombocytopenia, patients with active infection including CMV were excluded from the study. Patients with delayed graft function or rejection or any other complicating medical illness were excluded.

The treatment of TMA was not included in this analysis.

All patient characteristics including: age, sex, pre-transplant diagnosis, type of donor, induction therapy, maintenance therapy, time to developing thrombocytopenia, treatment given and the final results after three months of follow up were recorded. The above inclusion criteria were taken as a reference for including the patients as cyclosporine induced TMA. The data analyzed using Statistical Package for the Social Sciences version 22.

Results

Out of 1020 cases of kidney transplant, fifteen patients were diagnosed at Hawler teaching hospital- Kidney disease center with CsA-TMA.

The prevalence of CsA-TMA was 1.73%, of which 4(26.7%) were male while 11(73.3%) were female with male to female ratio of 1:2.75 and mean age ±standard deviation of 36.87±10.927.

Table (1): Gender distribution of patients with cyclosporine induced thrombotic microangiopathy, n=15.

Gender	No.	%
Male	11	73.3
Female	4	26.7
Total	15	100

Chronic glomerulonephritis constitutes the most frequently distributed type of pre-transplant diagnosis 5 (33.3%), followed by Focal segmental glomerulosclerosis (FSGS) 4 (26.7%) and diabetes mellitus 3 (20%). Others constitute the least frequent type 1 (6.7%), Table 2.

Table (2): Type of pre-transplant diagnosis, type of donor and induction therapy of patients with cyclosporine induced thrombotic microangiopathy, n=15.

Types of pre-transplant diagnosis	No.	%
Chronic glomerulonephritis	5	33.3
FSGS	4	26.7
Diabetes mellitus	3	20
Unknown	1	6.7
Polycystic kidney disease	1	6.7
Membranous nephropathy	1	6.7
Total	15	100

Figure 1 shows types of donors, live related was the maximum frequent 10 (67%) while live unrelated is the minimum frequent 5 (33%).

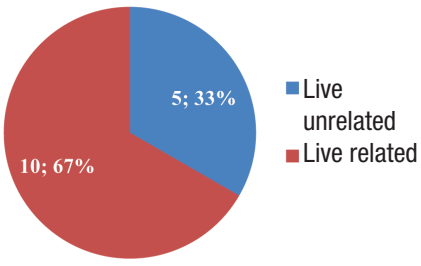

Figure (1): Type of donor, n=15.

More than half of the cases 8 (53%) received ATG as an induction therapy versus Basiliximab with 7 (47%), Figure 2.

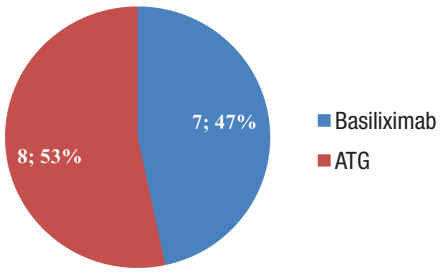

Figure (2): Induction therapy, n=15.

Regarding the days after transplant hemolytic uremic syndrome, the minimum was 5 days and maximum was 78 days with mean of 27.73 ± SD of 21.740 days.

Table 3 shows the laboratory findings of patients with cyclosporine induced thrombotic microangiopathy, n=15.

Table (3): Laboratory findings of patients with cyclosporine induced thrombotic microangiopathy, n=15

Laboratory tests	N	Minimum	Maximum	Mean	Std. Deviation
Serum creatinine peak (mg/dl)	15	1.1	3.8	2.247	0.853
Platelet count	15	10000	90000	47000	26063.110
Serum lactic dehydrogenase	15	714	1480	981.93	207.157
Serum hptoglobin (mg/dl)	15	6	35	19.86	10.167
Reticulocyte count (%)	15	3	16	9.60	4.469

Regarding serum lactic dehydrogenase and serum haptoglobin levels, it's found that all 15 cases developed high level S. LDH, meanwhile only 12 patients (80%) of them showed low leveln S. HGL.

Table (4): Serum haptoglobin category of patients with cyclosporine induced thrombotic microangiopathy, n=15

Serum haptoglobin level	No.	%
Low level	12	80.0
Normal level	3	20.0
Total	15	100

Discussion

Although the association between TMA and CsA is well established, medical literature on CsA-associated TMA in renal allografts is not abundant. Our review demonstrated only three studies based on a series of more than 10 patients[7, 15-21]. Our series of 1020 renal graft recipients with 15 patients diagnosed as CsA-associated TMA possibly constitutes the largest study published to date. CsA-associated TMA is not exclusive to renal allografts. The medical literature documents CsA-associated TMA in native kidneys of patients receiving CsA for the treatment of diseases such as uveitis and psoriasis[2, 5] and for non-renal allografts[3, 9, 11, 14]. It has been estimated that the frequency of TMA in bone marrow transplant recipients is between 6 and 26%[22].

The exact incidence of CsA-associated TMA in renal graft recipients is not known, as renal biopsy is the only available method of diagnosis of TMA, and indications for renal biopsy vary among medical centers. In this series of renal allograft recipients treated over a three-year period, TMA was diagnosed in 1.4% (15 of 1020) of the patients. At Tulane Medical Center, renal graft biopsies are obtained for renal graft dysfunction (a rise in serum creatinine of 0.5 mg/dl or greater above baseline), and protocol biopsies are not performed. All our TMA patients had an acute rise in serum creatinine of greater than 0.5 mg/dl above baseline without significant systemic symptoms. The post-transplantation time when TMA was diagnosed in our patients (from 5 to 78 days) had a wider range than has been previously described by others[7].

In most studies of renal graft recipients, as in ours, the occurrence of de novo TMA is associated with the use of CsA. The exception is a series of patients reported by Hourmant et al and reviewed by Colvin as acute idiopathic microangiopathy[23-25]. Hourmant et al reviewed 1378 patients who received renal allografts between 1979 and

1993 and observed TMA in 17 patients [24]; the presentation of the TMA episode was during the first three post-transplantation months, and none of the patients had TMA or hemolytic uremic syndrome before transplantation. Of the 17 patients with TMA, 13 were not on CsA at the time of the diagnosis of TMA. These findings are in distinct contrast to our experience and that published by others, since all of our TMA patients were on CsA.

The mechanisms of CsA-associated TMA are not well understood. Clinical and animal data show that CsA may have direct toxic effects on the endothelium. In a study using bovine aortic endothelial cells in culture, Zoja et al demonstrated that exposure to CsA induces direct cytotoxicity[26]. These investigators observed that CsA exposure of endothelial cells results in lactate dehydrogenase (LDH) release and dose- and time-dependent increases in generation of thromboxane A2 and prostacyclin. CsA therapy has been associated with an increased incidence of both arterial and venous thrombosis in the renal grafts[18]. Furthermore, CsA has been shown to increase adenosine diphosphate-induced platelet aggregation, thromboplastin generation, and factor VII activity, all participants in the pathogenesis of microangiopathy. Also relevant is the vasoconstrictor effect of CsA, shown in a rat model to be selectively more potent in the afferent glomerular arteriole. Although renin-angiotensin and atrial natriuretic hormone responses have been implicated in both experimental animals and in human graft recipients, a definitive role for increased renin axis could not be demonstrated[18]. An increase in trans-membrane flux of calcium causing vascular hyperre-activity has been postulated, supported by clinical data suggesting beneficial effects for calcium-channel blockers. Almost all of our patients, however, were on calcium antagonist, which did not appear to confer protection against CsA-associated TMA. It can be hypothesized that the elevated levels of endothelin in the blood and urine of patients receiving CsA 26-28 may initiate an intense vasoconstriction leading to endothelial damage, the apparent precursor lesion of TMA. When available, the newer endothelin receptor antagonists may be used to test the hypothesis[29, 30].

Conclusions

Thrombotic microangiopathy is a well-known complication of Cyclosporine. Paying attention to signs of hemolysis and thrombocytopenia in the blood film are important clues in detecting early the diagnosis.

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