

Thrombotic Microangiopathy in Renal Allografts

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The term “thrombotic microangiopathy” (TMA) encompasses non-inflammatory small vessel vasculopathies that are caused by severe endothelial and medial smooth muscle cell injury/necrosis. TMAs can be promoted by a variety of “toxic” stimuli ranging from malignant range hypertension, *E. coli* infections with bloody diarrhea, radiation, systemic diseases such as scleroderma to iatrogenic events such as the administration of drugs (e.g. calcineurin inhibitors, OKT3 or sirolimus, Table 1).

Causes of TMA	
<ul style="list-style-type: none">• Idiopathic• Autoimmune Diseases<ul style="list-style-type: none">– Systemic Lupus Erythematosus (SLE / APS)– Scleroderma• Malignant Hypertension• Enterohemorrhagic <i>E. coli</i> – HUS D+<ul style="list-style-type: none">– (typically <i>E. coli</i> 0157:H7)• Other infectious agents<ul style="list-style-type: none">– <i>Streptococcus pneumoniae</i>– HIV/AIDS• Abnormal vWF cleavage typical TTP	<ul style="list-style-type: none">• Pregnancy/ Postpartum<ul style="list-style-type: none">– (HELLP syndrome)• Drug Therapy<ul style="list-style-type: none">– <u>Chemotherapy (mitomycin, cisplatin, bleomycin etc)</u>– Immune mediated drug toxicity (quinine, ticlopidine, clopidogrel)– <u>Immunosuppressive drugs (FK 506/ cyclosporine)</u>– Contraceptives• Radiation (Dotatoc)• Bone marrow / peripheral stem cell transplantation

Table 1: Selected causes of thrombotic microangiopathies

Based on the morphologic examination of tissue sections, the specific triggering events of TMAs can often not be definitively identified making close clinico-pathologic correlations for adequate patient management mandatory. Depending on the type, degree, and stage of injury (early versus late), affected vessels show marked intimal swelling, extravasation of fragmented red blood cells into vascular walls, sometimes thrombus formation, influx of myofibroblasts into intimal layers, accumulation of fibrillary collagens, and (ultimately) irreversible hyalinosis or (concentric) intimal sclerosis (Figures 1 and 2). TMAs, regardless of the disease stage (early versus late), result in varying degrees of stenosis, impaired blood flow, and ischemic tissue injury. In severe cases even frank parenchymal necrosis can be observed. TMAs are frequently (but not always) generalized diseases commonly affecting the brain, pancreas, GI tract and

kidneys. TMAs in patients with marked neurologic symptoms are often classified as “thrombotic thrombocytopenic purpura”, i.e. TTP, whereas those with renal failure are commonly termed “hemolytic uremic syndrome”, HUS. Although different pathophysiologic events may indeed result in either TTP or HUS, these terms are typically not sharply separated in routine clinical practice, and the same patient may be labeled as “HUS” by the nephrologists and “TTP” by the hematologists. Of note: localized TMAs only affecting the kidneys occur. Such localized “vasculopathies” are often not associated with systemic symptoms, such as fragmentation of red blood cells, hemolysis, anemia, or thrombocytopenia (see below). Localized TMAs are more commonly seen in renal allografts. In the kidney (native and transplant) interlobular arteries, afferent arterioles and glomerular capillaries are typically affected. Glomerular lesions are characterized by endothelial cell injury, i.e. endotheliosis, occasional thrombus formation, and subendothelial new basement membrane formation resulting in global or segmental duplication of glomerular basement membranes (Figure 3 and 4).

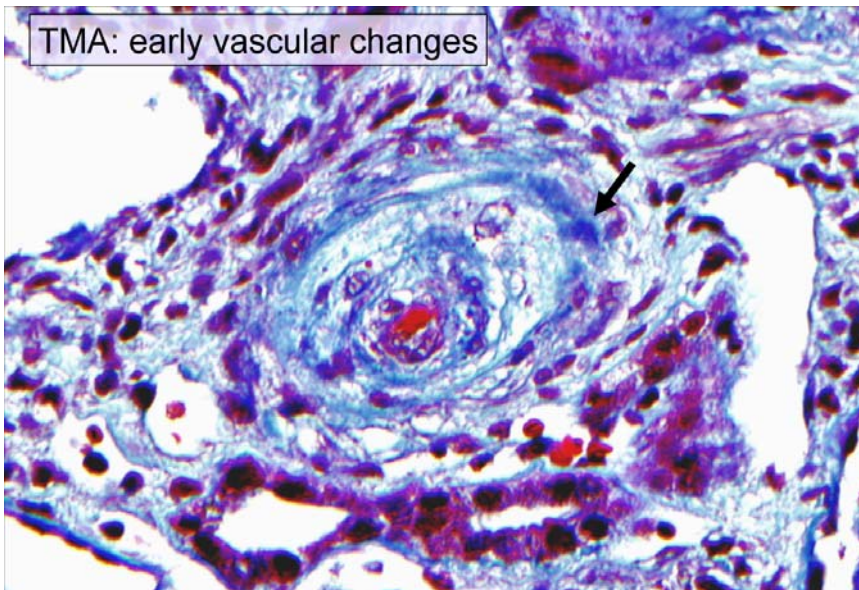


Figure 1: TMA (early arteriolar injury and remodeling) in a patient with malignant range hypertension. This case is characterized by marked intimal edema and severe stenosis. The arrow points towards hyaline nodules in the medial smooth muscle layer representing foci of single smooth muscle cell necrosis. Trichrome stain.

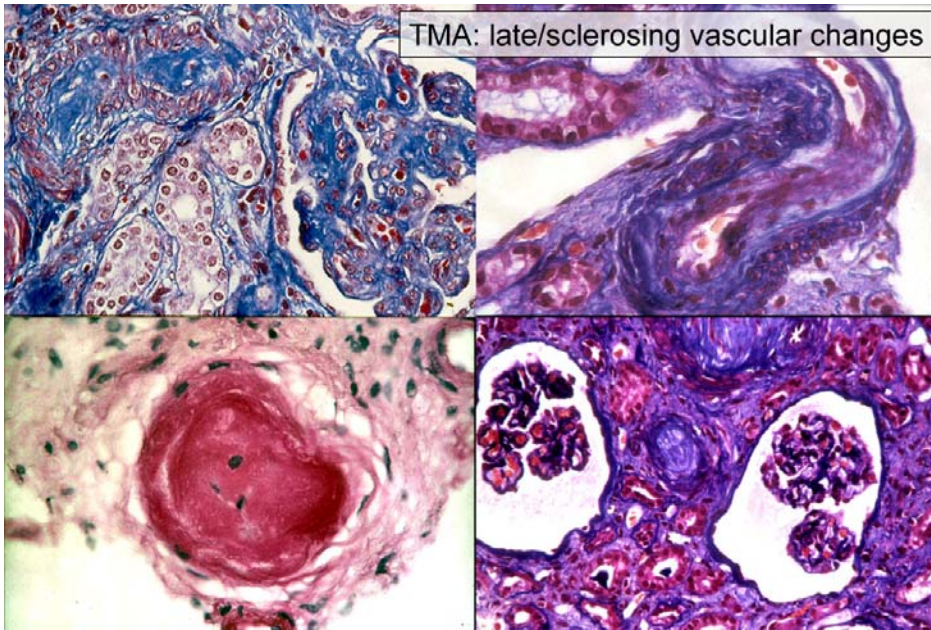


Figure 2: TMA (late arterial injury) with either marked, stenosing intimal sclerosis or occlusive hyalinosis (left lower image). Glomeruli, in particular in the right lower image, demonstrate ischemic tuft atrophy. PAS and trichrome stains.

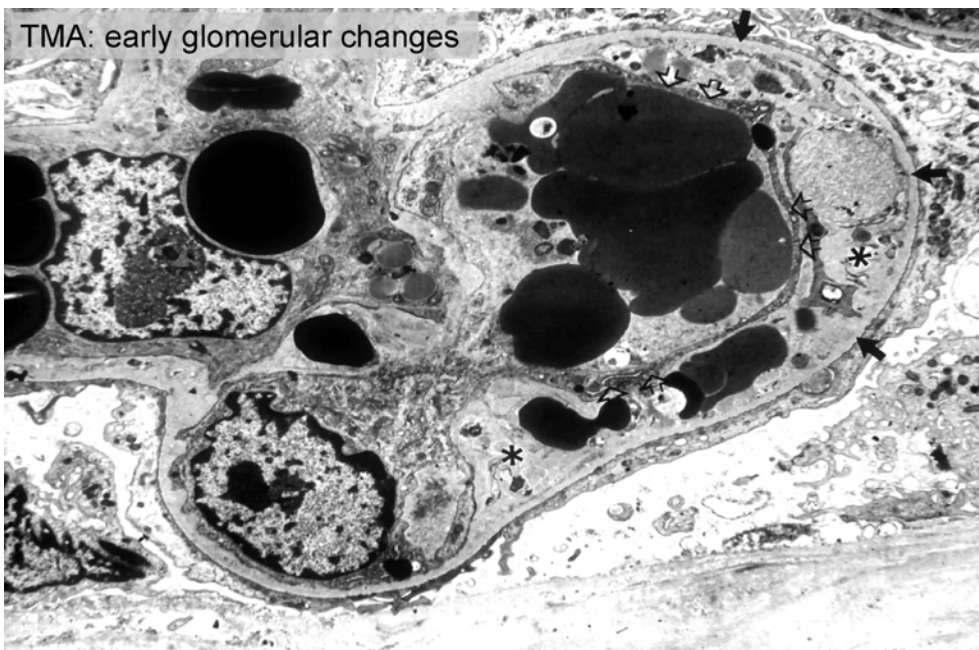


Figure 3: TMA (early glomerular injury). The arrowheads mark injured endothelial cells. Under the endothelial cell layer a newly formed subendothelial compartment is observed (asterisks) filled with partially fragmented red blood cells. Electron microscopy.

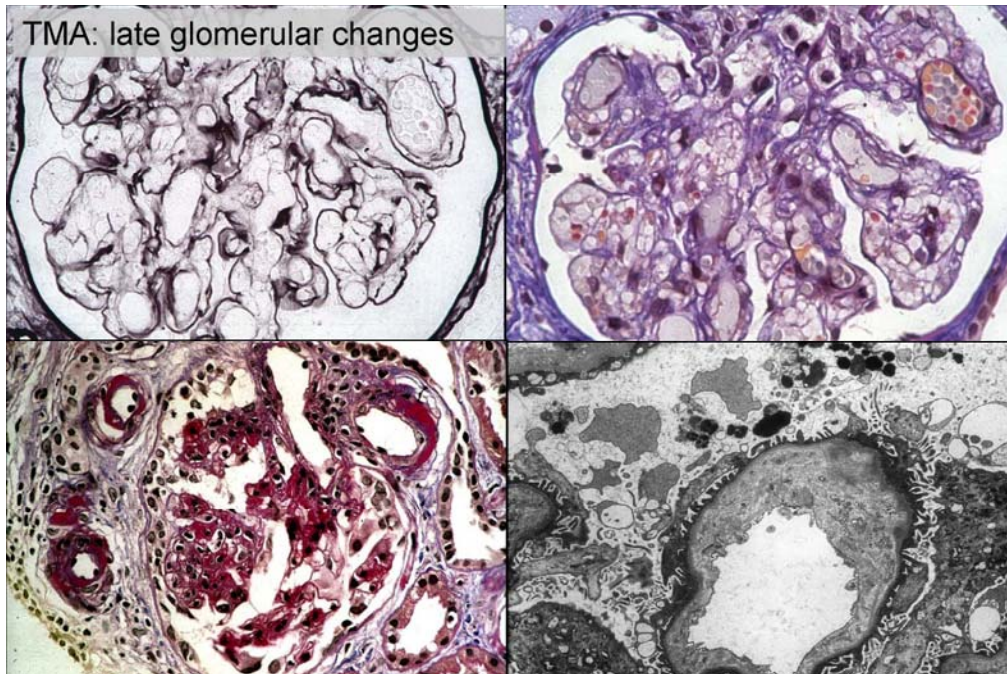


Figure 4: TMA (late glomerular injury). Glomerular capillary tufts show signs of mesangiolytic changes (upper right) and marked GBM remodeling with duplication. Segmental sclerosis (lower left) can occasionally be seen as a secondary phenomenon. Silver, trichrome, and PAS incubations, electron microscopy.

TMA can affect native kidneys and renal allografts alike. In a kidney transplant recipient certain “transplant specific” aspects have to be considered when entertaining the diagnosis of “TMA”:

- 1) Therapy with calcineurin inhibitors is often causative. Organ limited TMAs can show focal and relatively minor histologic changes.
- 2) Severe forms of a TMA may occur de-novo –or- may potentially reflect recurrent disease.
- 3) Antibody mediated rejection episodes have to be ruled out.

Ad 1) Most structural nephrotoxic effects of calcineurin inhibitors in arterioles and glomeruli (caused by either cyclosporine A or tacrolimus; 1) may best be regarded as manifestations of thrombotic microangiopathies, with different patterns and grades of severity (2, 3). They range from mild, focal and organ limited forms (hyaline arteriopathy) to florid cases of a generalized TMA/HUS (Table 2). Mild and limited forms are without great clinical significance; they are completely or partially reversible on dose reduction. Severe variants with fully developed, systemic thrombotic microangiopathies can result in graft failure or even patient death.

Both calcineurin inhibitor arteriopathy and glomerulopathy can develop within days to a few weeks, rendering terms such as “acute” and “chronic” toxicity inaccurate.

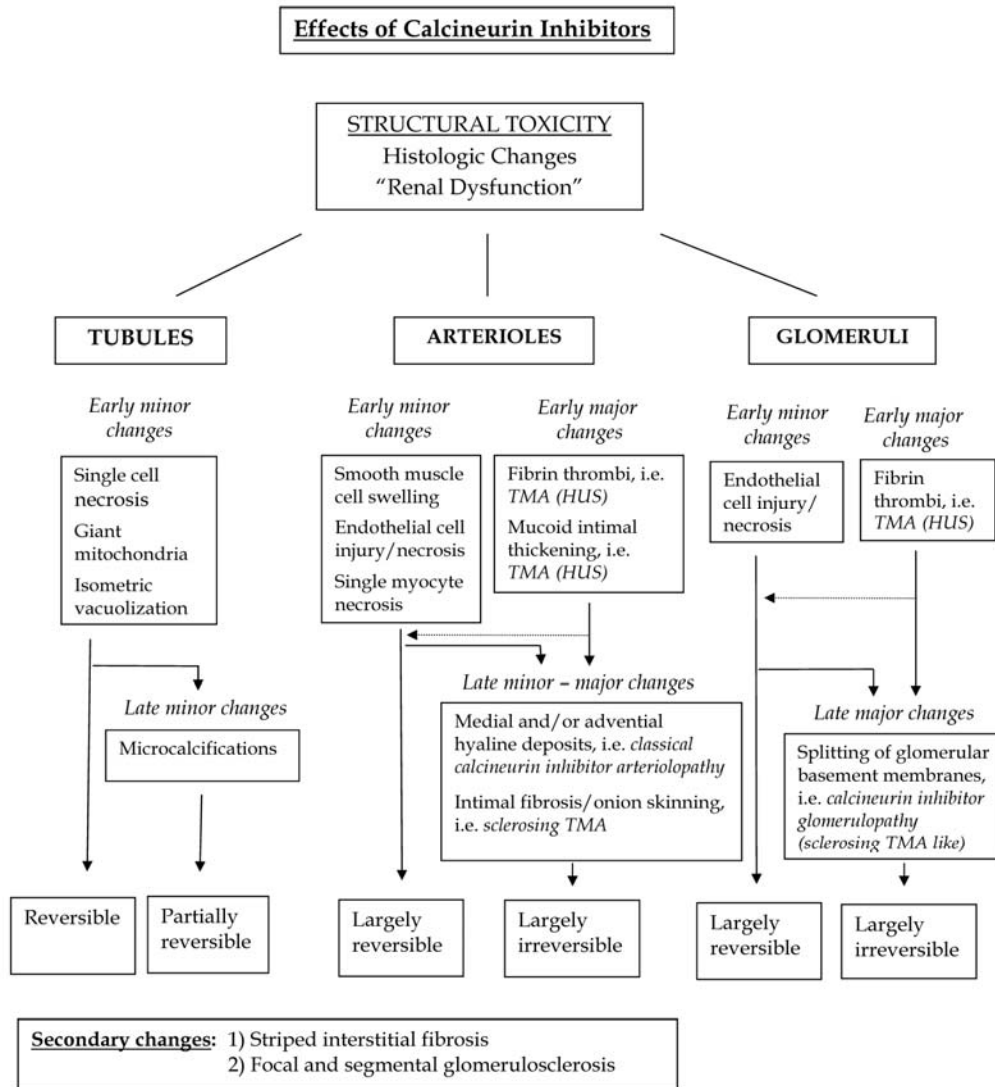


Table 2: Schematic of calcineurin inhibitor induced structural toxicity. Minor and major changes in arteries and glomeruli represent a continuum with overt TMA/HUS as the most severe adverse event.

From "Heptinstall's Pathology of the Kidney", chapter 28 (R.B. Colvin, V. Nickleleit: Renal Transplant Pathology, pages 1347-1490), 6th edition, J.C. Jennette, J.L. Olson, M.M. Schwartz, F.G.Silva eds, Wolters Kluwer publishing company, Philadelphia, 2007.

Calcineurin inhibitor-induced TMA is generally an early event occurring within the first few weeks post-grafting (range 2 to 56 days) (4, 5, 6) with only sporadic cases seen after months (7, 8). Although the precise mechanisms are not known, a causal role of cyclosporine A (CsA) or tacrolimus is clear in that rechallenge with a calcineurin inhibitor can precipitate a disease recurrence (9). As already indicated above, in kidney transplant recipients, the TMA may be limited to the renal allograft without systemic symptoms (10). Such limited form was observed in 38% of cases (8/21) in one series and associated with 100% graft survival (11). The incidence of TMA has been diminishing since CsA was initially introduced (12). CsA-associated thrombotic microangiopathy caused graft loss in 8% of 200 consecutive renal allografts in the early 1980s (accounting for 40% of those that failed) (13). Series of patients from the last 20 years reported an incidence of 0.9% to 14.1% (4, 6, 10, 11, 14 – 16), representing 26% of all cases of thrombotic microangiopathy after renal transplantation (acute rejection, probably humoral, accounted for 53% and recurrent thrombotic microangiopathy for 16%) (14). TMA-like changes have been reported with a prevalence of 1% to 4.7% in patients under tacrolimus therapy (7, 17, 18).

The treatment of calcineurin inhibitor-induced thrombotic microangiopathies includes the discontinuance or reduction of CsA/tacrolimus (sometimes with switch to sirolimus), and occasionally plasmapheresis, intravenous immunoglobulin, or thrombolytic agents (5, 6, 16, 19), with an overall graft salvage rate of 80 to 90% (4, 5, 19). If outcome is stratified into renal limited forms of a TMA and systemic generalized variants, graft survival rates were 100% in the former group (with reduction, temporary discontinuation, or conversion of calcineurin inhibitor therapy) and 62% to 90% in the latter cohort (including plasmapheresis as a treatment option) (11, 16). Calcineurin inhibitor induced TMA is (sometimes) fully reversible with the resolution of fibrin thrombi and restitution ad integrum, as demonstrated in 27% of grafts in one study (Table 2; 4). TMAs that are primarily affecting the glomeruli and spare arteries and arterioles fare better than those with pronounced vascular involvement. However, outcome data are not uniformly encouraging with graft failure rates reaching 31% in some series (10). 30% of patients presenting with a TMA after liver transplantation died (20). Interestingly, most renal transplant recipients (60 to 90%) tolerate the reintroduction of calcineurin inhibitors following the diagnosis and therapy of a TMA (4, 5, 16, 21-24); 25% were successfully converted to tacrolimus, with an overall salvage rate of 92% (22). It is curious that switching from CsA to tacrolimus is sometimes successful even through both drugs act via very similar pathways (10, 15, 25).

Ad 2) TMA recurred in 41% of 17 patients at the University of Minnesota, based on strict clinical and histologic features (26). Other series have reported frequencies of 15% to 29% (27, 28, 29). The cause of the original TMA influences recurrence, with the highest rate seen in familial forms (approximately 100%) (30) and scleroderma (31), and the lowest (approximately 0%) in HUS/TMA associated with E. coli infections (32). Recurrent disease typically becomes manifest during the first year post grafting with symptoms noted as early as the first post operative day. The diagnosis of recurrent TMA is difficult because de novo variants in the transplant have an identical pathology (e.g.,

calcineurin inhibitor, sirolimus or OKT3 induced). A focal distribution pattern may favor a diagnosis of calcineurin inhibitor-induced toxic injury, and the lack of C4d deposition excludes acute humoral rejection. Whether therapy with calcineurin inhibitors and/or sirolimus, which can cause TMA, is a risk factor for disease recurrence has been debated; clearly recurrence is seen in the absence of these drugs (33, 34). In classical HUS (with bloody diarrhea, D+), patients seem to benefit from CsA therapy, which resulted in increased graft survival in one study (32). The recommended treatment for recurrent TMA is intensive plasmapheresis combined with administration of fresh frozen plasma, as in the primary disease (35). Recurrent TMA causes graft loss in most patients (70%).

Patient	Age (y)	Sex	Race	End-Stage Renal Disease Diagnosis	Type of Transplant	No. of Transplants	Loss From TMA	Follow-Up (mon)	Local v Systemic	Cause
1	47	M	C	Type 1 diabetes	CAD	1	No	55	L	TAC
2	24	F	C	Type 1 diabetes	SKP	1	No	84	L	TAC
3	33	M	AA	Chronic glomerulonephritis	CAD	1	No	94	L	CSA
4	57	M	AA	Type 2 diabetes	LD	1	No	32	L	TAC
5	40	M	C	Type 1 diabetes	CAD	1	No	26	L	TAC
6	42	M	AA	Hypertensive nephrosclerosis	CAD	1	No	70	L	CSA
7	46	M	C	Renal cell carcinoma	CAD	1	No	75	L	CSA
8	47	F	C	Polycystic	LD	1	No	29	L	Unknown
9	38	F	C	Polycystic	CAD	1	Yes	68	S	CSA
10	30	F	C	Reflux nephropathy	CAD	1	No	26	S	TAC
11	28	M	C	Pauci-immune glomerulonephritis	CAD	1	Yes	15	S	Unknown
12	49	M	C	Type 1 diabetes	CAD	1	Yes	44	S	TAC
13	49	M	AA	Hypertensive nephrosclerosis	CAD	1	Yes	27	S	TAC
14	56	F	H	Chronic glomerulonephritis	CAD	1	No	137	S	CSA
15	43	F	C	Interstitial nephritis	CAD	1	No	93	S	CSA
16	46	M	C	Chronic glomerulonephritis	CAD	1	No	27	S	TAC
17	35	F	C	Renal cell carcinoma	CAD	2	No	156	S	CSA
18	50	F	C	Polycystic	LD	1	No	35	S	TAC
19	42	F	C	ImmunoglobulinA nephropathy	CAD	1	No	23	S	TAC
20	31	F	C	Type 1 diabetes	CAD	1	Yes	11	S	CSA
21	40	M	C	Chronic glomerulonephritis	CAD	1	Yes	39	S	CSA

Abbreviations: C, Caucasian; AA, African American; H, Hispanic; CAD, cadaveric transplant; LD, living donor; SKP, simultaneous kidney pancreas transplant; L, local; S, systemic.

Table 3: TMA post transplantation (from ref. 11)

Ad 3) Antibody mediated rejection episodes may occasionally mimic TMAs including thrombus formation in small vessels (such as glomerular capillaries) or fibrinoid vascular wall necrosis in most severe cases. In these cases the detection of the complement degradation product C4d along peritubular capillaries can help since approximately 90% of antibody mediated rejection episodes are C4d positive whereas cases of TMAs are characteristically C4d negative (36, 37). Only approximately 10% of antibody mediated rejection episodes are C4d negative, sometimes due to unusual circulating antibodies such as those directed against angiotensin receptors (36-38). In these latter cases close clinico-pathologic correlation and additional serologic studies are required in order to render a definitive diagnosis.

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