Thrombotic microangiopathy and the kidney: a nephropathologist's perspective

Anthony Chang

Abstract

Thrombotic microangiopathy is a common renal pathologic finding, which is characterized by the presence of endothelial cell injury and microvascular thrombi. The spectrum of clinical diseases that are connected by a thrombotic microangiopathic injury may appear to be unrelated, but overactivation of the complement system is emerging as an important mechanism, especially in atypical haemolytic uraemic syndrome, antiphospholipid antibody syndrome, HELLP syndrome, and others. Although few pathologic findings enable the pathologist to establish the precise aetiology of the microvascular injury, kidney biopsy remains the gold standard for diagnosing renal thrombotic microangiopathy and excluding other potential causes of kidney injury. After this critical step, additional investigation of the clinical and laboratory data is necessary to establish the underlying aetiology and guide subsequent therapeutic options. The salient clinical and pathologic features of common diseases that are associated with thrombotic microangiopathy will be discussed.

Keywords alternative complement pathway; antiphospholipid antibody syndrome; haemolytic uraemic syndrome; malignant hypertension; scleroderma; thrombocytopenic purpura

Introduction

Thrombotic microangiopathy (TMA) is a common cause of acute kidney injury that manifests with microvascular thrombi and can be observed in association with a diverse set of clinical settings (Table 1) either as the predominant injury or possibly secondary to other primary glomerular diseases. When TMA persists and becomes chronic, there may be a multilayering of capillary basement membranes with a paucity of thrombi. Clinical findings of TMA include thrombocytopenia and haemolytic anaemia with schistocytes that may be visualized on the peripheral blood smear. The pathologist is generally unable to establish the precise aetiology of the microvascular injury based on the biopsy findings alone, so additional correlation with clinical and laboratory data is necessary for the treating physician to establish the aetiology of the TMA.

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Endothelial cell injury is a common mechanism that links the different clinical entities that are associated with TMA. In addition, based on recent studies, improper regulation of the alternative pathway of the complement system is emerging as an important contributing factor for many etiologies of TMA. Severely decreased levels of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) can also be frequently observed. Therefore, it is important for the pathologist to be familiar with the various clinical entities that are associated with TMA.

Histopathology of TMA

Acute TMA can be diagnosed when thrombi are identified in renal arteries, arterioles, or glomerular capillaries (Figure 1). Thrombi distend the lumen of the involved vessel and often contain entrapped red blood cells or their fragments. When the thrombi are located in the glomerular capillaries, there is no gap between the thrombus and capillary wall a feature that contrasts with hyaline "thrombi" or pseudothrombi, such as those seen in lupus nephritis or cryoglobulinemic glomerulonephritis, which have a homogeneous staining quality and often reveal artifactual separation of the glomerular capillary wall from the prominent aggregate of immune complexes. On one occasion, I have observed the cytoplasm of a proximal tubular epithelial cell within a glomerular capillary, which mimicked an intracapillary thrombus. An immunohistochemical stain for CD10 confirmed that the lesion was indeed a proximal tubular epithelial cell, which must have been artifactually placed in the capillary during the biopsy procedure or tissue processing. Severe arteriolar hyalinosis as observed in diabetic nephropathy can appear to occlude the entire lumen, but the staining quality is very homogeneous, which is distinct from true thrombi in TMA. Immunohistochemistry for CD61, which is also known as integrin β3 or glycoprotein IIIa, can confirm the presence of platelets (Figure 2) within the thrombi, although this is generally not necessary to establish the diagnosis of TMA. In contrast, arteriolar hyalinosis will be negative for CD61 immunohistochemistry. When the thrombi involve the hilar arterioles or if there is prominent endothelial cell swelling, the glomeruli can acquire a "bloodless" appearance. Mesangiolysis may occur. Prominent tubular injury that is secondary to the vascular injury is often present and even necrosis can be observed, which is predictive of a poor outcome.

In the acute injury phase, detachment of the endothelial cell from the glomerular basement membranes (GBM) is first noted by electron microscopy (Figure 3). When the endothelial cell injury becomes chronic, there is duplication of the GBM, because the endothelial cell and visceral epithelial cell (podocyte) produce material that contributes to the formation of the GBM. When TMA persists, the endothelial cell continues to produce basement membrane material after it detaches from the GBM, which results in a second layer or duplicated GBM, (Figure 4). However, there may be entrapment of IgM and C3 within the duplicated basement membranes. Usually the intensity of immunofluorescence staining is modest and discrete electron dense deposits are not prominent; nonetheless this finding may mimic immune complex deposition. Multilayering

Clinical settings that may manifest with TMA

Haemolytic uraemic syndrome
Thrombotic thrombocytopenic purpura
Malignant hypertension
Disseminated intravascular coagulation
Anti-phospholipid antibody syndrome
Scleroderma
Pregnancy-associated TMA
Pre-eclampsia
Eclampsia
HELLP syndrome
Radiation nephropathy/haematopoietic cell transplantation
Sickle cell nephropathy
Pharmacologic agents
Chemotherapeutic agents
Anti-VEGF inhibitors (sunitinib, sorafenib, bevacizumab)
Rifampin
Quinine
Calcineurin inhibitors (cyclosporine, sirolimus, tacrolimus)
Antibody-mediated rejection

Table 1

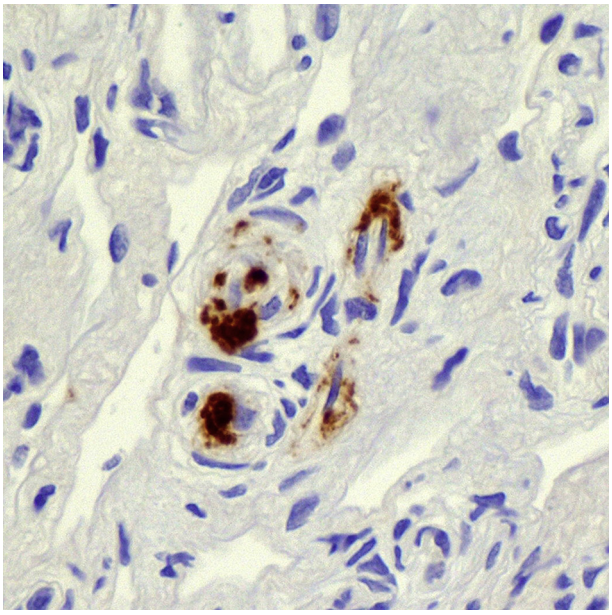

Figure 2 CD61 immunohistochemistry reveals aggregates of platelets within an arteriole containing a thrombus. TMA is a light microscopic diagnosis, which generally does not require confirmation with this ancillary study. Arteriolar hyalinosis, which appears distinct from TMA, will not demonstrate any CD61 staining.

of the peritubular capillary basement membranes is observed with chronic antibody-mediated rejection, but this finding may also be present with other diseases that manifest with chronic TMA.

Myxoid alteration of the intima (Figure 5) of small or large arteries with entrapped red blood cell fragments or leukocytes is often observed in TMA, which is frequently accompanied by a clinical history of severe (or malignant) hypertension or scleroderma renal crisis, and should result in closer scrutiny of a pathologic specimen for additional evidence of TMA. Immunofluorescence microscopy for fibrinogen (Figure 6) will strongly stain thrombi, if present. However, the arterioles with pathologic alterations may also demonstrate entrapment of IgM and C3 within the lumen or vessel walls.

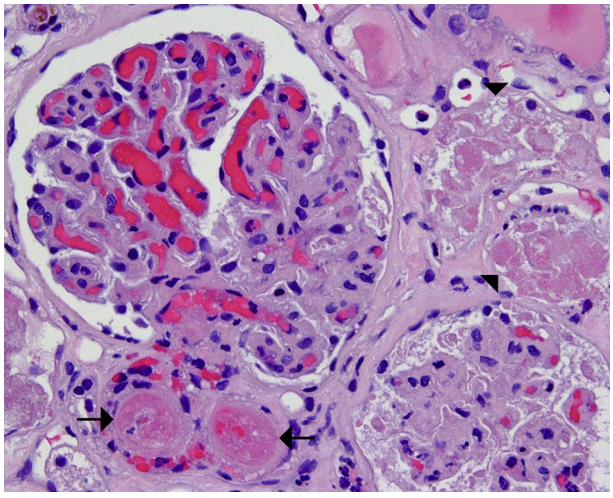

Figure 1 Thrombi (arrows) occlude the lumen of an arteriole and contained some entrapped red blood cells. Adjacent proximal tubules demonstrate necrosis with detachment of cells (arrowheads) from the tubular basement membranes into the tubular lumina (H&E).

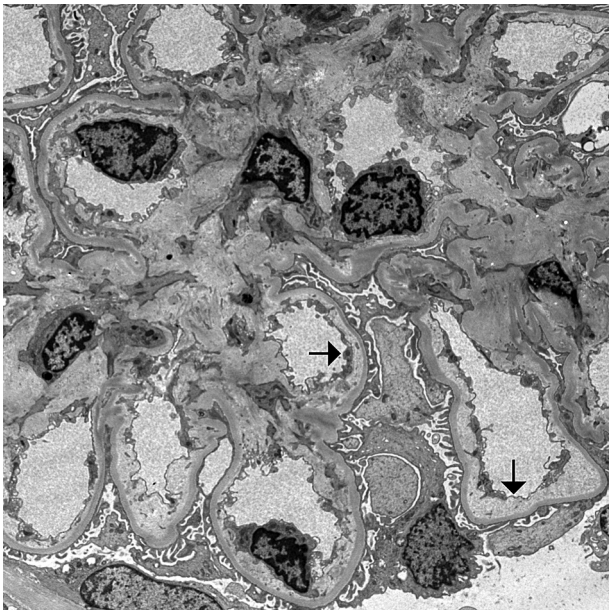

Figure 3 Electron microscopy shows marked detachment or separation of the endothelial cell in nearly every glomerular capillary from the glomerular basement membrane (arrows) with subendothelial space widening by electron lucent material. As this injury persists, a second or duplicated layer of the glomerular basement membrane may form, but this is not apparent in this photomicrograph, which suggests that this example may be in the acute injury phase.