

*Teaching Point*  
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## tHe USual Suspects

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### Introduction

Hypertensive changes on fundoscopy are a common finding in renal patients, given the high prevalence of hypertension in this population. We report the interesting case of a 71-year-old man with known pancreatic adenocarcinoma who was referred by our ophthalmology colleagues with Grade IV hypertensive retinopathy, severe hypertension and renal impairment.

### Case

A 72-year-old man presented with a short history of headaches with reduced visual acuity in his right eye. His general practitioner then referred him to the ophthalmologist who found Grade IV hypertensive retinopathy with bilateral papilloedema on fundoscopy. He was referred to a medical team for further assessment.

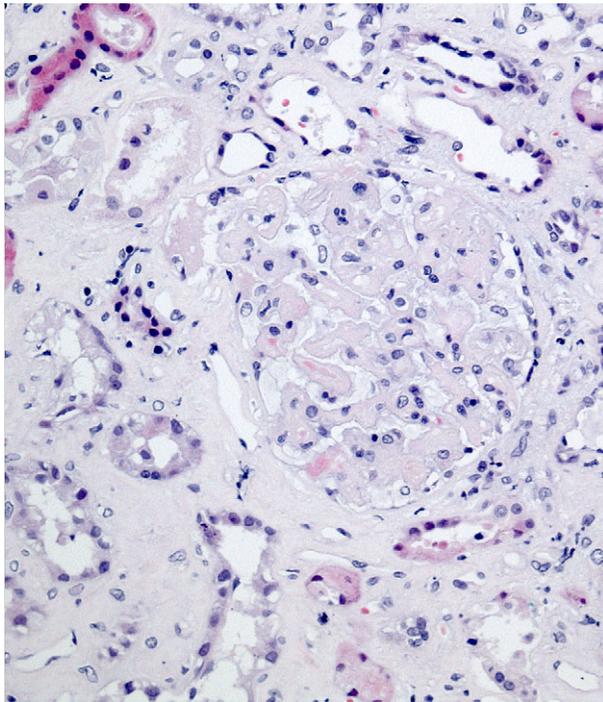
Eleven months prior to this current presentation, the patient developed painless jaundice, pale stools and weight loss. Computed tomography revealed a 7-cm mass in the pancreas. Intraoperatively, metastatic deposits were discovered in the small bowel mesentery. Palliative gastroenterostomy, bilioenteric anastomosis and enteroenterostomy were performed. Histology confirmed adenocarcinoma. He underwent seven monthly cycles of Gemcitabine chemotherapy, the last of which was 6 weeks prior to his current admission.

On admission, his blood pressure was 210/124 mmHg. There was reduced air entry and dullness to percussion bibasally on examination of the chest. Chest X-ray showed cardiomegaly and bilateral effusions. An electrocardiogram showed evidence of left ventricular hypertrophy. A recent echocardiogram had shown mild left ventricular impairment as well as a pericardial effusion that was not haemodynamically relevant. An ultrasound

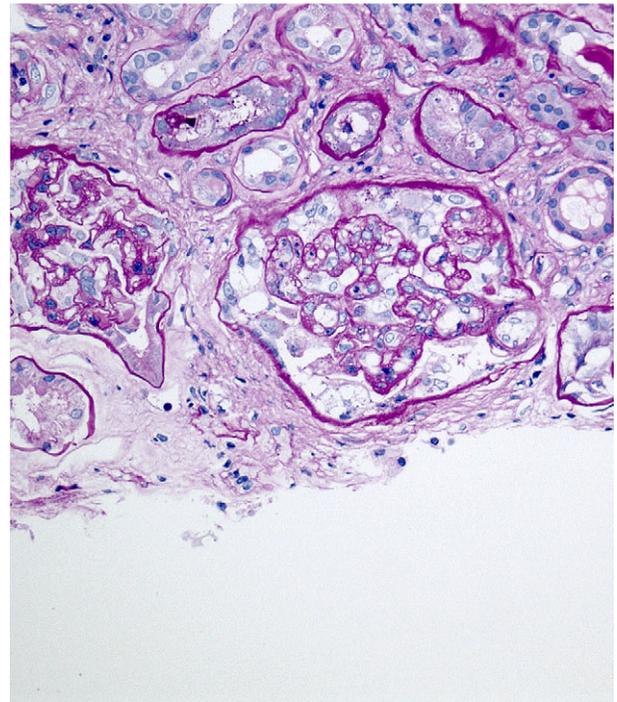
scan showed normal-sized kidneys without chronic parenchymal changes. Serum biochemistry revealed evidence of acute kidney injury, with serum creatinine 230  $\mu\text{mol/L}$  (1 month previously serum creatinine had been within normal range). The urinary protein creatinine ratio was 470 mg/mmol creatinine. Full blood count showed anaemia and thrombocytopenia (haemoglobin 8.8 g/dL, white blood count  $8.8 \times 10^9/\text{L}$ , platelets  $70 \times 10^9/\text{L}$ , reticulocyte count 3.7%). The serum lactate dehydrogenase was markedly elevated at 1919 U/L and serum haptoglobin was  $<0.01$  g/L consistent with haemolysis. The blood film revealed fragmented red blood cells. Serum immunoglobulins and complement C3 and C4 were normal. Anti-neutrophil cytoplasmic antibodies, anti-neutrophil antibodies and antibodies to extractable nuclear antigens, including Scl-70, were all negative. A renal biopsy was performed.

The biopsy showed some glomeruli with increased mesangial matrix and eosinophilic material in the capillary lumina, indicating intraluminal thrombus (Figure 1). Periodic acid-Schiff stain showed a fibrillary appearance of the mesangium (Figure 2). Silver stain showed focal splitting of the glomerular basement membrane. A diagnosis of thrombotic microangiopathy with renal involvement was made and both the underlying malignant disease and the chemotherapy with Gemcitabine were seen as possible underlying causes. Gemcitabine was stopped. Plasma exchange was briefly considered but not done after a review of the evidence. Treatment with amlodipine and atenolol was started to control blood pressure. An assay of von Willebrand factor-cleaving protease came back as normal, as did assays for Factors H and I. *Escherichia coli* 0157:H7 serology was positive. The patient had no diarrhoea at this point in time nor did he recall any previous episode of loose stools. Stool culture was negative.

The patient did well subsequently and he was discharged from hospital. When last seen in clinic, he was well with stable renal function (serum creatinine 289  $\mu\text{mol/L}$ ). He is under regular review by the oncology team, currently there is no evidence of disease progression and no further chemotherapy is planned.



**Fig. 1.** Renal biopsy showing thickening of glomerular capillary walls and capillary thrombi (haematoxylin and eosin, original magnification  $\times 20$ ).



**Fig. 2.** Renal biopsy demonstrating reduplication of the glomerular basement membrane. Some areas of the glomerulus have a fibrillary appearance (periodic acid-Schiff, original magnification  $\times 20$ ).

## Discussion

Microangiopathic haemolytic anaemia with thrombocytopenia, acute kidney injury of varying degrees of severity, neurologic abnormalities and fever are key features of thrombotic microangiopathy (TMA). It is now rare to see the full pentad of findings to be present in the same individual. Histologically, TMA is characterized by the formation of microthrombi within the affected organs. The classical phenotypes of haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) describe two extremes of what is now regarded as a spectrum of clinical variants under the umbrella term TMA. Of note, there is considerable inconsistency in the nomenclature and consensus in this regard is lacking.

There are a number of different recognized causes of TMA (Table 1). Our patient had been diagnosed with advanced pancreatic adenocarcinoma during the year prior to his current presentation. Advanced solid organ malignancy is a well-described cause of TMA [2]; the course of this type of TMA is often refractory to treatment. No particular malignancy is particularly associated with TMA but the occurrence of TMA often indicates advanced cancer. TTP-HUS is also a recognized complication of a number of treatments for cancer, most notably haematopoietic stem cell transplantation (HSCT) and chemotherapy. The TMA variant associated with HSCT remains particularly poorly understood and many novel treatment options have been tried, such as defibrotide.

With regard to chemotherapy, several regimes have been associated with TMA, including Cisplatin, Mitomycin C and Gemcitabine. To what extent the drug itself (and not

the underlying malignancy) is responsible for the occurrence of TMA is not always clear [3]. In our case, the onset of the microangiopathic haemolytic anaemia occurred after seven monthly cycles of Gemcitabine. We were interested to encounter this drug in the context of TMA, as one of us had seen a similar case previously [4]. Gemcitabine is actually a well-described and recognized cause of TMA. The effect appears to be dose dependent and the disease tends to be insidious in onset, often occurring months after the chemotherapy has been discontinued [5, 6]. How drugs such as Gemcitabine cause TMA is essentially unclear although one may postulate that the chemotherapy agents cause damage to the endothelium, perhaps with some degree of individual susceptibility and/or genetic background. Recent research has shed some light on the mechanisms of and susceptibility for TMA.

In health, ultralarge von Willebrand factor multimers are released in response to endothelial injury. These thrombogenic glycoproteins are normally cleaved by a protease, ADAMTS13. If the activity of ADAMTS13 is reduced either due to an inherited deficiency or due to autoantibodies then thrombotic microangiopathy can occur [7]. Treatment of these TMA subtypes with plasma exchange is usually very effective. We found no evidence of any defect in the von Willebrand factor-cleaving protease in our patient. It is also important to remember that blood samples for such tests need to be sent prior to the first session of plasma exchange in patients in whom such treatment is undertaken.

Complement dysfunction is another underlying mechanism in some cases of TMA and mutations in complement Factor H, Factor I, Factor B and membrane cofactor protein

**Table 1.** Causes of thrombotic microangiopathy: mechanism, diagnosis and management. [1]

TMA subtype	Mechanism	Diagnosis	Treatment
Diarrhoea-positive HUS	Shiga-like toxin	<i>E. coli</i> 0157:H7 serology Stool culture	Mainly supportive
Classical TTP	Inherited or acquired deficiency of ADAMST13	ADAMST13 level and function, ADAMST13 antibodies	Plasma exchange is usually very effective
Familial TMA	Genetic disorder in complement Factors H, I, B, MCP	Gene mutational analysis	Plasma exchange
Drugs (Cisplatin, Mitomycin C, Gemcitabine; Ticlopidine, Clopidogrel; Cyclosporin, Tacrolimus; Quinine)	Unknown	Drug history	Stop offending drug
Malignancy	Unknown	Consider imaging in refractory TMA of unknown origin Blood culture	Treat underlying disease Poor prognosis
Neuraminidase producing organisms ( <i>Streptococcus pneumoniae</i> , Influenza)	Unknown	Pneumococcal antigen	Antibiotics/ antivirals Consider plasma exchange
Human immunodeficiency virus infection	Unknown	Serology	Antiretroviral therapy Plasma exchange

have all been described. The outcome after renal transplantation varies greatly between different defects so it is important to identify which is responsible [8]. Unfortunately, these tests remain costly and time consuming. In our case, complement levels and Factors H and I were normal.

Infection with Shiga-like toxin producing *E. coli* 0157:H7 has been known to cause TMA since the 1980's, commonly in children and in the elderly. In our case, *E. coli* 0157:H7 serology came back as positive. It is conceivable that subclinical infection may have contributed to the occurrence of TMA in our case [9]. The mechanism of this subtype of TMA is well understood: Shiga-like toxin produced by *E. coli* 0157:H7 translocates across the colonic wall into the bloodstream and eventually binds to Gb3 receptors expressed on renal endothelial cells [10]. This leads to inhibition of protein synthesis, subsequent cell death and the formation of microthrombi. Management is mainly supportive.

It is also important to remember that several disorders can mimic TMA, most notably malignant hypertension, scleroderma and the antiphospholipid antibody syndrome (APS) [1]. Laboratory tests allowed us to exclude scleroderma and APS. In our case, the findings on biopsy were diagnostic of TMA: histological changes in malignant hypertension are often focal, with many glomeruli appearing relatively unchanged. Arteries will show intimal hyperplasia, medial hypertrophy and splitting of internal

elastic lamina, but not widespread microthrombi as seen in our case.

The treatment of TMA remains difficult in many patients, especially those who do not fit the classical TTP or HUS phenotype. The response of vascular markers in peripheral blood to plasma exchange predicts the success of this treatment [11]. A clinical trial with a novel monoclonal antibody targeted against C5, eculizumab, is currently underway. There is limited evidence that plasma exchange is of benefit in the management of Gemcitabine-induced TMA [12, 13]. Rituximab has been employed in this setting with reported success anecdotally [14, 15].

## Conclusions

Our patient initially presented with headaches and hypertensive retinopathy, and we expected to see yet another case of hypertensive nephropathy. We were surprised to watch more and more clues emerge, leading to a diagnosis of TMA. During the course of our investigation, we managed to round up some of 'the usual suspects' for TMA. In doing so, we felt reminded of Bryan Singer's 1995 American neo-noir film that carries the same title. A critic commented on this movie that in the end the whole thing played back in one's mind in perfect clarity. We felt the same about this case that had so puzzled us initially, and enjoyed this detour into the differential diagnosis of TMA, as well as the way it all came together in the end.

## Teaching points

- (1) In the assessment of a TMA, a number of causes need to be considered as they have implications for management.
- (2) The presence of one obvious cause of TMA does not exclude other contributing factors.
- (3) Advanced malignancy, treatment with Gemcitabine, and *E. coli* 0157:H7 infection are all implicated in the development of TMA.
- (4) Recent research has improved our understanding of TMA and novel treatment options are also on the horizon.

*Conflict of interest statement.* Dr A.W. received consulting fees from Alexion UK, the manufacturer of eculizumab, in January, 2011. He has no other involvement with the company. The other authors declare no conflict of interest.

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