# ANCA-negative Pauci-immune Crescentic Glomerulonephritis with Thrombotic Microangiopathy

**Dear Editor,**

Pauci-immune crescentic glomerulonephritis (Pauci-immune CGN) is the most common cause of CGN. Thrombotic microangiopathy (TMA) defines a clinicopathological syndrome consisting of intraluminal platelet thrombosis in the microvasculature and the presence of fragmented red blood cells and thrombocytopaenia in the peripheral blood, and may be seen in haemolytic uraemic syndrome (HUS), thrombotic thrombocytopaenic purpura (TTP) and other conditions. Co-existence of TMA and pauciimmune CGN is rare. We describe a case of anti-neutrophil cytoplasmic antibody (ANCA)-negative pauci-immune crescentic glomerulonephritis with microangiopathic haemolytic anaemia and histopathological evidence of TMA.

**Case Report**

A previously healthy 73-year-old Chinese male presented with progressive pallor and jaundice associated with decreased effort tolerance over a period of 1 to 2 weeks. There was transient antecedent fever. His blood pressure was 150/80 mmHg on admission. He was found to have Coombs-negative anaemia associated with schistocytes, low haptoglobin, increased reticulocytes and marginal thrombocytopaenia, consistent with microangiopathic haemolytic anaemia. His renal function deteriorated rapidly over 3 weeks (the serum creatinine concentration increased from 223 μmol/L to 926 μmol/L) at which point a renal biopsy was performed. He was also found to have an exudative pericardial effusion and pleural effusion. There was also a mild transient increase in the serum liver aminotransferase concentration. The serum C3 concentration was low while the C4 concentration was borderline. Serum ANCA (anti-PR3 and anti-MPO), cryoglobulin and autoimmune markers (including antinuclear, anti-mitochondrial, anti-dsDNA, anti-Smith, anti-LKM, anti-cardiolipin antibodies and rheumatoid factor) were negative.

The patient was treated with pulsed intravenous methylprednisolone, cyclophosphamide and oral prednisolone. Haemodialysis was started for uraemia and fluid overload. Four weeks following admission, he developed haemoptysis with increasing breathlessness and anaemia. He was transferred to the intensive care unit (ICU) and supported with mechanical ventilation. Unfortunately, he passed away after an intractable cardiac arrhythmia. No lung biopsy was obtained and an autopsy was not performed.

The renal biopsy showed a crescentic glomerulonephritis. Nine of 17 non-obsolescent glomeruli showed cellular or fibrocellular crescents (Figs. 1a and 1b), 7 of which also showed segmental necrosis. A few glomeruli showed thrombi within their capillaries (Fig. 1a). The glomeruli without crescents as well as the unaffected segments of the glomeruli with crescents were relatively unremarkable, with no increased cellularity or endocapillary proliferation. One arteriole showed segmental transmural inflammation and thrombosis (Fig. 1c).

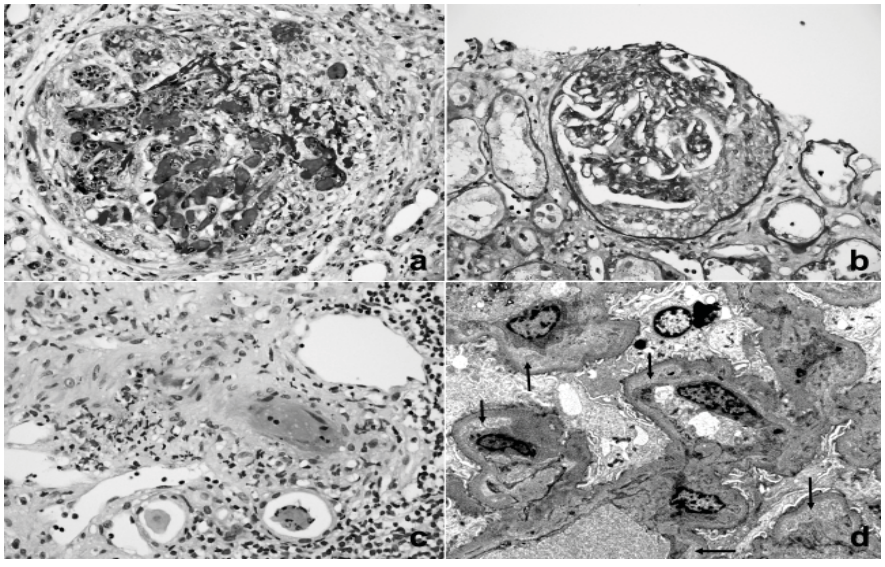


Fig. 1. (a) A glomerulus with a cellular crescent and with thrombi within the capillary loops (Masson trichrome stain, original magnifi cation x 400). (b) Another glomerulus with a cellular cresecent, showing glomerular tufts that were relatively unremarkable, without increased cellularity or endocapillary proliferation (Periodic acid-Schiff stain, original magnifi cation x 400). (c) An arteriole with transmural infl ammation and thrombosis (Haematoxylin & Eosin, original magnifi cation x 400). (d) Electron micrograph of a glomerulus showing capillary loops with an expanded subendothelial zone containing granular to 'fluffy' material of intermediate electron density (arrows). (Electron microscopy, original magnifi cation, x 7800).

Immunofluoresence microscopy showed weak discontinuous fi ne granular mesangial and capillary loop staining for IgG, IgM and Kappa and Lambda light chains. In addition, there was moderate segmental granular capillary loop and mesangial staining for fi brin. No signifi cant staining for IgA, C1q and C3 was seen. There was no linear capillary loop staining for IgG or C3 to suggest anti-glomerular basement membrane disease.

Ultrastructural examination showed glomerular capillary loops with expanded subendothelial zones containing granular to 'fluffy' material of intermediate electron density (Fig. 1d). No subendothelial electron dense deposits or mesangial interposition was identified.

Overall, the features were those of a pauci-immune crescentic glomerulonephritis, ANCA-negative type. However, the presence of fibrin thrombi within the glomeruli and the widespread lucent subendothelial zones on electron microscopy, coupled with clinical evidence of microangiopathic haemolytic anemia, indicated the concomitant presence of thrombotic microangiopathy.

## Discussion

Many publications equate pauci-immune CGN with ANCA-associated CGN. However, ANCA has been found to be negative in a substantial number of patients with pauci-immune CGN,[1,2] and clinico-pathological features of ANCA-negative cases were comparable with those of ANCA-positive disease.[1,3] What was intriguing in this case was the concomitant presence of clinical and histopathological evidence of TMA. Although small crescents may occasionally be present in HUS, CGN is generally not seen in TMA alone. Furthermore, vasculitis with acute infl ammatory infi ltrate is not a feature of TMA.Hence, it seemed more probable that TMA and pauci-immune CGN in our case occurred as concurrent disease processes.

The co-occurrence of TMA or HUS and pauci-immune CGN is rare. Only a few cases have been reported so far[4-6] (Table 1). This may be related to the facts that both HUS/TTP and pauci-immune CGN are uncommon disorders, and that while pauci-immune CGN is more common in patients over 60 years of age, HUS/TTP rarely occurs in this age group. Stefanidis et al[4] described a case of c-ANCA-positive CGN in which the pre-glomerular arterioles showed subendothelial edema, infiltration of fragmentocytes and fibrointimal narrowing, but there were no glomerular ultrastructural changes of TMA. Hirsch et al[5] described a case with glomerular and arteriolar changes of TMA on light and electron microscopy associated with crescent formation and positive serum p-ANCA titres. Lastly, Green et al[6] reported a case of biopsy-diagnosed pauci-immune CGN in which clinical and haematologic manifestations of HUS developed 2 months later. The serum ANCA titre in this case was not known. All these cases mentioned above showed evidence of microangiopathic haemolytic anemia, but no definite aetiologic association between TMA and CGN could be concluded. Our case appears unique, since the pauci-immune CGN was ANCA-negative. Since both pauci-immune CGN and TMA might be triggered by infectious or inflammatory stimuli in the presence of predisposing factors, it might be possible that a common event contributed to development of both disorders, in a rare case where predisposition to both disorders were present. Indeed, our patient had an episode of increased serum liver aminotransferase concentration that spontaneously resolved, and this might represent an insult, like hepatitis, that had preceded his renal failure and possibly acted as a trigger. On the other hand, it was possible that TMA preceded the pauci-immune CGN, and contributed to pro-infl ammatory mediators, like TNFα, that might be released due to endothelial damage, resulting in priming of neutrophils and neutrophil activation by ANCA or ANCA-like factors.

Table 1. Summary of the Features of Previously Reported Cases of Co-occurrence of TMA/HUS and Pauci-immune Crescentic Glomerulonephritis, along with the Current Case

| Reported cases | Serum ANCA titre status | ANCA type | Renal biopsy findings | |
|---|---|---|---|---|
| | | | Glomerular changes of TMA | Extraglomerular vascular changes of TMA |
| Stefanidis et al[4] | Positive | c-ANCA | Not identified | Present (seen on LM) |
| Hirsch et al[5] | Positive | p-ANCA | Present (seen on EM) | Present (seen on LM) |
| Green at al[6] | Not known | NA | NA* | NA* |
| Current case | Negative | NA | Present (seen on LM and EM) | Present (seen on LM) |

TMA: thrombotic microangiopathy; HUS: haemolytic uraemic syndrome; ANCA: anti-neutrophil cytoplasmic antibody; LM: light microscopy; EM:electron microscopy; NA: not applicable

*The clinical and haematologic features of TMA/HUS manifested 2 months after the renal biopsy was performed.

The possibility of pauci-immune CGN triggering TMA or a TMA-like response seems less likely, based on epidemiological evidence.

## Conclusion

The importance of diagnosing both TMA and pauci-immune CGN is more than academic. Although both HUS/TTP and pauci-immune CGN may be treated by immuno-suppression and plasma therapy, plasma exchange is life-saving in TTP and indicated in adult HUS, while immunosuppression is the mainstay of treatment for pauci-immune CGN. Hence, accurate diagnosis of both conditions will allow the best possible therapy to be tailored for the patient, especially when one mode of therapy appears to be ineffective.

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Chee Leong Cheng,[1] *MBBS, FRCPath*, Lee Ying Yeoh,[2] *MD, MRCP*, Veerasamy S Selvan,[2] *MBBS, MRCP*, Thomas P Thamboo,[3] *MBChB, FRCPath, FRCPA*

[1]Ministry of Health Holdings Pte Ltd, Singapore
[2]Department of Internal Medicine, Alexandra Hospital, Singapore
[3]Department of Pathology, National University Hospital, Singapore

Address for Correspondence: Dr Thomas Paulraj Thamboo, Department of Pathology, National University Hospital (Level 3), Lower Kent Ridge Road, Singapore 119074.
Email: Thomas_Paulraj_Thamboo@nuhs.edu.sg