CASE REPORT

A rare case of thrombotic microangiopathy triggered by acute pancreatitis

Kevin Singh,[1] Ahmed Jamal Nadeem,[1] Behzad Doratotaj[2]

[1]Department of Medicine, New York University School of Medicine, Woodhull Medical and Mental Health Center, Brooklyn, New York, USA
[2]Department of Haematology and Oncology, New York University School of Medicine, Woodhull Medical and Mental Health Center, Brooklyn, New York, USA

Correspondence to
Dr Kevin Singh,
Singh.kevin@gmail.com

Accepted 27 April 2017

SUMMARY

Thrombotic microangiopathy (TMA) occurring after acute pancreatitis is rarely described. Without prompt intervention, TMA can be, and often is, lethal, so prompt recognition is important. Here, we present a case of a 61-year-old woman with a history of alcohol misuse who presented with epigastric pain, nausea and vomiting after binge drinking. Elevated serum lipase and imaging were suggestive of acute-on-chronic pancreatitis. Although the patient's symptoms of acute pancreatitis subsided, her anaemia, thrombocytopenia and acute kidney injury worsened. A peripheral blood smear revealed schistocytes, prompting suspicion for TMA. Therapeutic plasma exchange (TPE) was promptly initiated and she completed 10 TPE sessions that improved her anaemia and serum creatinine and resolved the thrombocytopenia. Since TPE was effective and the ADAMTS13 assay revealed 55% activity in the absence of anti-ADAMTS13 IgG prior to initiation of therapy, a confident diagnosis of TMA caused by acute pancreatitis was made. There was no evidence of relapse 2 years later.

BACKGROUND

Thrombotic microangiopathy (TMA) describes a group of disorders that share a common clinical presentation: microangiopathic haemolytic anaemia (MAHA) defined as haemoglobin (Hb) <10 g/dL accompanied by evidence of haemolytic anaemia; thrombocytopenia (platelet count <150x10^9/L) and end-organ dysfunction that in many cases presents as acute kidney injury (AKI; as defined by Kidney Disease: Improving Global Outcomes guidelines).[1 2] Although the differential diagnosis of MAHA, thrombocytopenia and AKI is vast and includes common systemic disorders such as sepsis and malignant hypertension, the differential should always include TMA syndromes because of the significant morbidity and mortality associated with these conditions. Of these syndromes, the 'primary' syndromes include thrombotic thrombocytopenic purpura (TTP), Shiga toxin-mediated TMA (ST-TMA) and TMA associated with complement dysregulation or coagulopathy, and 'secondary' syndromes that are associated with known precipitating factors.[3]

ST-TMA accounts for 90% of cases in children and is caused by infection with *Escherichia coli* O157:H7 ST-producing organisms. The annual incidence of ST-TMA is 6.1 cases per 100 000 children younger than 5 years old, in contrast to the very rare incidence in adults (two cases per 100 000).[4] Since ST-TMA (previously known as typical hemolytic uremic syndrome (HUS)) is infrequently diagnosed in adults, the availability of epidemiological studies with mortality statistics is limited for this patient group, and the studies that do exist are heterogeneous in terms of HUS definition and aetiologies, restricting their use.[5] However, a population study reported that hospitalisations and deaths were most frequent in adults aged 60 years and older and the number of mortalities was 10-fold higher in this group than any other affected age group.[6]

Since ST-TMA is infrequently diagnosed in adults, the most frequent TMA syndromes encountered in this population are TTP (~25%), TMA associated with complement dysregulation or coagulopathy (~20%) and secondary TMA syndromes (~55%).[3] Unlike ST-TMA, these TMA syndromes tend to have a more aggressive course with frequent relapses and a higher mortality rate if treatment is not promptly started, mainly due to end-stage renal disease,[7–9] which is more common in adults and the elderly compared with children. This finding may be explained by underdiagnosis of TMA in adults, in whom comorbidities and risk factors for chronic kidney disease (CKD) such as hypertension and diabetes mellitus or pre-existing CKD exist.[5]

TMA is associated with acute pancreatitis in <1% of the total population.[10] Although TMA can precipitate acute pancreatitis in 2% of TMA cases, the presentation of acute pancreatitis preceding TMA is even less common.[11 12] Here, we present a case of TMA in a patient initially managed for acute-on-chronic pancreatitis. Due to the high mortality rate of patients with TMA and renal failure serving as a poor prognostic factor in acute pancreatitis, this case is a reminder of this unique presentation, its pathogenesis and management so that the diagnosis is promptly recognised.

CASE PRESENTATION

A 61-year-old African-American woman with a history of alcohol misuse presented with a 6-day history of sharp epigastric pain, nausea and vomiting after a binge-drinking episode. The pain radiated to her back without any subjective precipitating or relieving factors. There was no history of diarrhoea or constipation. The patient reported that she had abstained from alcohol for 5 years but, due to recent stressors, she had recently started to binge drink again with an approximate daily consumption of 750 mL of vodka. Prior to this recent binge-drinking episode, she had a 10-year history of alcohol misuse

To cite: Singh K, Nadeem AJ, Doratotaj B. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2016-218581

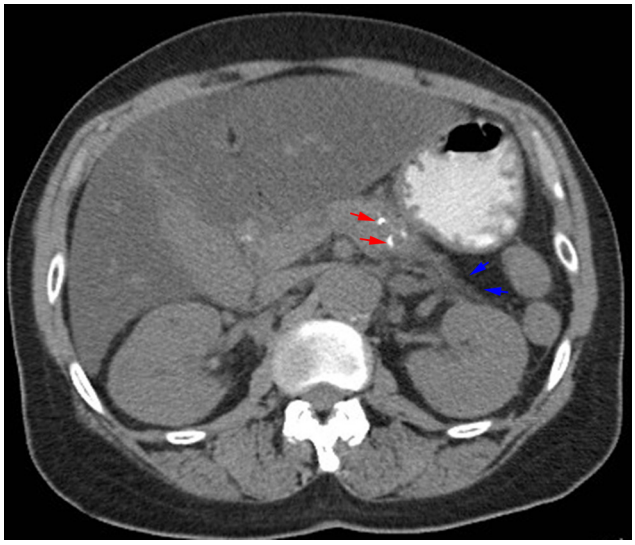

Figure 1 Abdominal CT scan showing calcification of the pancreatic parenchyma (red arrows) and acute inflammatory changes involving the tail of the pancreas with peripancreatic fluid (blue arrows).

and consumed an estimated 7–8 beers for 3–4 days per week with complications including four prior episodes of alcohol-induced acute pancreatitis. She denied taking any medications or drugs of abuse.

INVESTIGATIONS

At presentation, her body temperature was 36.7°C, blood pressure 146/86 mm Hg, heart rate 85 beats per minute and oxygen saturation 98% on air. Palpation of the epigastric region and right upper quadrant elicited pain but physical examination was otherwise unremarkable. Preadmission laboratory studies were: Hb 12.2 g/dL (12.0–16.0 g/dL), platelet count 276x10^9/L (130–400x10^9/L), blood urea nitrogen 48 mg/dL (8–26 mg/dL), serum creatinine 2.2 mg/dL (0.8–2.0 mg/dL), serum calcium 9.8 mg/dL (8.5–10.5 mg/dL), aspartate transaminase 112 U/L (0–40), alanine transaminase 37 U/L (0–45 U/L), lactate dehydrogenase (LDH) 281 U/L (80–200 U/L), lipase 1254 U/L (8–78 U/L) and serum triglyceride 71 mg/dL (30–200 mg/dL). Urinalysis did not reveal any haematuria, proteinuria, pyuria or bacteria, but the urine was concentrated with a specific gravity of 1.030. Urine toxicology was negative for amphetamines, cannabinoids, cocaine, opiates and phencyclidine. An abdominal CT scan revealed acute inflammatory changes in the head of the pancreas extending to the tail and splenic hilum, peripancreatic fluid and calcification of the pancreatic parenchyma (figure 1). Abdominal ultrasound did not reveal the presence of gallstones.

The serum creatinine improved with intravenous hydration to 1.7 and 1.5 mg/dL on the first and second days, respectively. On the third day, the symptoms of acute pancreatitis had resolved and there was no evidence of alcohol withdrawal. However, at that time, the patient had developed anaemia: Hb 9.3 g/dL, reticulocyte production index 4.0% (0.5%–2.0%), total bilirubin 2.2 mg/dL (0.0–1.5 mg/dL), indirect bilirubin 1.8 mg/dL (0–1 mg/dL), haptoglobin 12 mg/dL (43-212) and LDH 1232 U/L. She had also developed thrombocytopenia with a platelet count of 25x10^9/μL and worsening AKI with the serum creatinine increasing to 1.8 mg/dL. Urinalysis at that time revealed 2+ blood, 3+ protein, a small amount of bilirubin and a specific gravity 1.010 in the absence of red blood cell casts, pyuria or bacteria. Renal ultrasound revealed normal-sized kidneys without nephrolithiasis or signs of urinary obstruction including hydronephrosis. These findings were suggestive of renal parenchymal injury without urinary obstruction.

DIFFERENTIAL DIAGNOSIS

Alcohol-induced acute-on-chronic pancreatitis with AKI was initially diagnosed. The acute anaemia appeared to be a secondary phenomenon and was haemolytic, supported by the elevated reticulocyte count, LDH, total and indirect bilirubin levels, decreased haptoglobin level and presence of schistocytes in the peripheral blood smear. The prothrombin (PT) time (10.6 s; 9.5–11.8 s), activated partial thromboplastin time (PTT) (23.7 s; 20.4–33.4 s), serum D-dimer (0.37 mg/dL; 0.19–0.50 mg/dL), fibrinogen (264.1; 166.3–472.7), C3 (100 mg/dL; 75–181), C4 (19.1 mg/dL; 14.0–45.0 mg/dL) and total complement activity (CH_{50}) (52 U/mL; 22–60 U/mL) were all normal and HIV and direct Coombs tests were negative. Given that the serum D-dimer, fibrinogen, PT and PTT were within normal limits, disseminated intravascular coagulation (DIC) was unlikely and because the stool culture did not grow ST-producing organisms, ST-TMA was unlikely. Thus, because of the high clinical suspicion for TMA related to acute pancreatitis with an unclear diagnosis of TTP, a serum sample was obtained to assess ADAMTS13 activity, which was 55% in the absence of IgG directed against ADAMTS13.

TREATMENT

Due to the high mortality rate of acute-on-chronic pancreatitis and the patient's comorbidities, she was admitted to the hospital, where she was monitored for alcohol withdrawal and received intravenous fluids and analgesia. After diagnosis of TMA, therapeutic plasma exchange (TPE) with fresh frozen plasma was initiated on day 4 of admission.

OUTCOME AND FOLLOW-UP

Prior to discharge on day 17, the patient underwent 10 TPE sessions, by which time the Hb was 9.6 g/dL, platelet count 346 x10^9/L, serum creatinine 1.6 mg/dL, LDH 207 U/L and the reticulocyte count and total bilirubin levels were normal (figure 2A–C). There was no evidence of relapse 2 years later.

DISCUSSION

Thirty-three cases of TMA preceded by acute pancreatitis are described in the literature, with gallstones and heavy alcohol consumption the most frequently reported triggers of acute pancreatitis in these cases.[9–21] Although the exact relationship between these two conditions is unclear, it is thought that cytokines such as interleukin-1 and tumour necrosis factor-α are released during acute pancreatitis, which cause vascular endothelial damage.[7 10 13] ADAMTS13, a plasma protease complex, prevents platelet aggregation in healthy patients by cleaving von Willebrand factor. However, during acute pancreatitis-related TMA, ADAMTS13 is inhibited by cytokines produced by ongoing inflammation, resulting in platelet aggregation and thrombus formation from shear stress on the vascular endothelium.[22] Unlike the severe ADAMTS13 deficiency seen in TTP (<10% activity), acute pancreatitis-related TMA may present with normal or low ADAMTS13 activity in the absence of anti-ADAMTS13 IgG antibodies, as seen here.[22 23]

TPE has been the first-line treatment for TMAs including TTP and HUS since 1980. TPE replaces ADAMTS13 and complement proteins and removes the cytokines that promote haemolysis, platelet aggregation and endovascular damage.[23–25] According

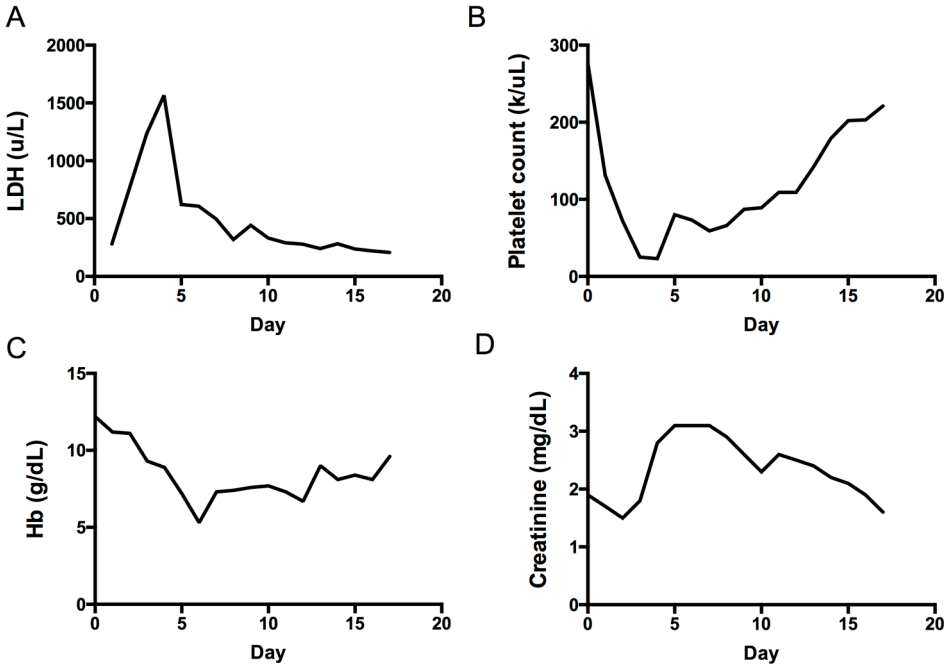

Figure 2 Biochemical and haematological progression over the course of admission. Plasma exchange was commenced on day 4. (**A**) Lactate dehydrogenase (LDH), a biomarker of haemolysis; (**B**) platelets; (**C**) haemoglobin (Hb); (**D**) creatinine.

to consensus opinion, a trial of TPE is recommended in all patients with a suspected diagnosis of TTP–HUS.[1 2 26] During TPE, the platelet count and markers of haemolysis such as Hb, LDH, indirect bilirubin levels and the reticulocyte count should be carefully monitored. This is because alternative treatments such as eculizumab, a human monoclonal antibody targeting C5, need to be considered if the platelet count does not recover or haemolysis does not resolve after three to five TPE sessions since complement-mediated TMA may need to be considered as an alternative diagnosis.[8 27–31] Haematological response is defined as normalisation of the platelet count without evidence of haemolysis for 2 days and remission is defined as a sustained response after cessation of TPE for at least 30 days.[1] Although renal function must be monitored closely, a lack of renal improvement should not change the overall management since patients may have sustained irreversible renal injury.[27]

Our patient initially presented with acute-on-chronic pancreatitis and AKI without evidence of anaemia or thrombocytopenia that would otherwise suggest TMA. We speculate that volume depletion, common in acute pancreatitis, caused the patient to initially develop AKI since there was prerenal azotaemia. With intravenous fluid hydration, her renal function improved on admission days 1 and 2 but started to deteriorate again on day 3. Given that there was AKI, acute haemolytic anaemia and thrombocytopenia, we suspected TMA in the differential diagnosis. However, considering that the mortality rate of untreated TTP is estimated as greater than 90% and there is overlap between the clinical presentations of the various TMA syndromes, we initiated TPE because of the unclear presumptive diagnosis.[32] The adequate response to TPE allowed us to continue with the treatment plan in spite of the fact that the ADAMTS13 activity was 55%—low but not severely deficient and in the absence of anti-ADAMTS13 IgG—making TTP an unlikely diagnosis. Furthermore, other conditions such as DIC, sepsis, inflammatory states and even healthy patients may have moderate ADAMTS13 deficiencies, but these states were ruled out in our patient.[33]

Since our patient improved with TPE, it was likely that our patient's clinical state was caused by secondary TMA associated with acute pancreatitis. Complement-mediated TMA was an unlikely diagnosis, and assessment for mutations was not pursued given these findings, lack of available testing in our institution and the low diagnostic sensitivity (50%) for known mutations that in most cases do not provide adequate clinical information about potential candidates for eculizumab.[31] Also, drug-related TMA was ruled out since there was no history of her taking medications known to cause TMA prior to admission or during the hospitalisation or any evidence of the use of illicit substances.[34]

Interestingly, our patient presented with an elevated blood pressure, a common initial sign of TMA that often manifests as new onset or an exacerbation of pre-existing hypertension. However, at presentation, there was no evidence of anaemia or thrombocytopenia or a hypertensive emergency (formerly known as malignant hypertension), which is a frequent cause of haemolytic anaemia, thrombocytopenia and AKI linked with TMA. Since our patient had moderate to severe thrombocytopenia (described as a platelet count of 20–50x10^9/L) without severe hypertension (defined as systolic blood pressure >200 mm Hg and diastolic blood pressure >120 mm Hg), it was unlikely that our patient's findings were caused by malignant hypertension that would have otherwise involved aggressive blood pressure control with antihypertensives, particularly renin–angiotensin system antagonists rather than the use of TPE.[35]

Like other reported cases, the diagnosis of TMA was made 3 days after initial diagnosis of acute pancreatitis, although some reported cases of TMA have been diagnosed up to 15 days later.[10] However, in the literature, only 3 out of 33 patients were aged 60 years and older and the cause of acute pancreatitis was described as idiopathic or gallstone related. Hence, this is the first case of alcohol-induced acute pancreatitis triggering TMA in an African-American woman who was over 60 years old.

Learning points

- Acute pancreatitis can lead to many complications including acute kidney injury (AKI).
- Although uncommon, new onset or worsening anaemia and thrombocytopenia in the presence of AKI should raise the suspicion of thrombotic microangiopathy (TMA) in patients diagnosed with acute pancreatitis.
- When TMA is suspected, therapeutic plasma exchange (TPE) should be initiated promptly since morbidity and mortality are high without timely intervention.
- Eculizumab can be considered in TMA that is refractory to TPE or as a first-line agent for complement-mediated TMA.

Contributors KS, AJN and BD all played a role in managing this patient when she was admitted to the hospital. KS wrote this manuscript and proofreading was completed by all authors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Scully M, Cataland S, Coppo P, *et al*. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. *J Thromb Haemost* 2017;15:312–22.
2 Go RS, Winters JL, Leung N, *et al*. Thrombotic microangiopathy care pathway: a consensus statement for the Mayo Clinic Complement Alternative Pathway-Thrombotic Microangiopathy (CAP-TMA) Disease-Oriented Group. *Mayo Clin Proc* 2016;91:1189–211.
3 George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. *Blood* 2010;116:4060–9.
4 Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med* 2009;361:1676–87.
5 Tostivint I, Mougenot B, Flahault A, *et al*. Adult haemolytic and uraemic syndrome: causes and prognostic factors in the last decade. *Nephrol Dial Transplant* 2002;17:1228–34.
6 Gould LH, Demma L, Jones TF, *et al*. Hemolytic uremic syndrome and death in persons with *Escherichia coli* O157:H7 infection, foodborne diseases active surveillance network sites, 2000–2006. *Clin Infect Dis* 2009;49:1480–5.
7 Conway EM. HUS and the case for complement. *Blood* 2015;126:2085–90.
8 Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis* 2011;6:60.
9 Chaturvedi S, Carcioppolo D, Zhang L, *et al*. Management and outcomes for patients with TTP: analysis of 100 cases at a single institution. *Am J Hematol* 2013;88:560–5.
10 Swisher KK, Doan JT, Vesely SK, *et al*. Pancreatitis preceding acute episodes of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: report of five patients with a systematic review of published reports. *Haematologica* 2007;92:936–43.
11 Boyer A, Chadda K, Salah A, *et al*. Thrombotic microangiopathy: an atypical cause of acute renal failure in patients with acute pancreatitis. *Intensive Care Med* 2004;30:1235–9.
12 Moulis G, Huart A, Forgues M, *et al*. [Acute pancreatitis and thrombotic microangiopathy: a two-way association]. *Nephrol Ther* 2012;8:20–2.
13 Fu P, Yuan AH, Wang CH, *et al*. Alcohol-induced severe acute pancreatitis followed by hemolytic uremic syndrome managed with continuous renal replacement therapy. *BMC Nephrol* 2014;15:1–3.
14 Malleshappa P, Chaudhari AP, Aghariya M, *et al*. Thrombotic microangiopathy as a complication of recurrent pancreatitis. *Indian J Nephrol* 2011;21:215–7.
15 Mijatovic D, Blagaic A, Zupan Z. Case Report: Severe form of hemolytic-uremic syndrome with multiple organ failure in a child: a case report. *F1000Res* 2014;3:79.
16 Jeliazkova P, Noe S, Jost P, *et al*. Postendoscopic retrograde cholangiopancreatography pancreatitis: a rare cause of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Eur J Gastroenterol Hepatol* 2011;23:825–7.
17 Taton O, Delhaye M, Stordeur P, *et al*. An unusual case of haemolytic uraemic syndrome following endoscopic retrograde cholangiopancreatography rapidly improved with eculizumab. *Acta Gastroenterol Belg* 2016;79:257–61.
18 Sinha A, Rai R. Haemolytic uraemic syndrome following acute pancreatitis. *JOP* 2005;6:365–8.
19 Silva VA. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome secondary to pancreatitis. *Am J Hematol* 1995;50:53–6.
20 Chang HH, Chen ML, Chang CC. Acute pancreatitis preceding an acute episode of thrombotic microangiopathy. *Clin Nephrol* 2010;73:244–6.
21 Piton G, Navellou JC, Morati P, *et al*. Thrombotic thrombocytopenic purpura associated with severe acute pancreatitis in a context of decreased ADAMTS13 activity: a case report. *Eur J Gastroenterol Hepatol* 2008;20:1226–30.
22 Mannucci PM, Peyvandi F. TTP and ADAMTS13: when is testing appropriate? *Hematology Am Soc Hematol Educ Program* 2007;2007:121–6.
23 Adamski J. Thrombotic microangiopathy and indications for therapeutic plasma exchange. *Hematology Am Soc Hematol Educ Program* 2014;2014:444–9.
24 Nguyen TC, Han YY. Plasma exchange therapy for thrombotic microangiopathies. *Organogenesis* 2011;7:28–31.
25 Saland JM, Ruggenenti P, Remuzzi G; Consensus Study Group. Liver-kidney transplantation to cure atypical hemolytic uremic syndrome. *J Am Soc Nephrol* 2009;20:940–9.
26 Nester CM, Thomas CP. Atypical hemolytic uremic syndrome: what is it, how is it diagnosed, and how is it treated? *Hematology Am Soc Hematol Educ Program* 2012;2012:617–25.
27 Zuber J, Fakhouri F, Roumenina LT, *et al*. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. *Nat Rev Nephrol* 2012;8:643–57.
28 Palma LM, Langman CB. Critical appraisal of eculizumab for atypical hemolytic uremic syndrome. *J Blood Med* 2016;7:39–72.
29 Mannucci PM, Cugno M. The complex differential diagnosis between thrombotic thrombocytopenic purpura and the atypical hemolytic uremic syndrome: laboratory weapons and their impact on treatment choice and monitoring. *Thromb Res* 2015;136:851–4.
30 Clark WF, Patriquin C, Licht C, *et al*. Simple diagnosis and treatment algorithm for adult thrombotic microangiopathy. *Transfus Apher Sci* 2017;56:50–1.
31 Cataland SR, Yang S, Wu HM. The use of ADAMTS13 activity, platelet count, and serum creatinine to differentiate acquired thrombotic thrombocytopenic purpura from other thrombotic microangiopathies. *Br J Haematol* 2012;157:501–3.
32 Amorosi EL, Ultmann JE. Thrombotic thromocytopenic Purpura: report of 16 cases and review of the literature. *Medicine* 1966;45:139–60.
33 Moore JC, Hayward CP, Warkentin TE, *et al*. Decreased von Willebrand factor protease activity associated with thrombocytopenic disorders. *Blood* 2001;98:1842–6.
34 Al-Nouri ZL, Reese JA, Terrell DR, *et al*. Drug-induced thrombotic microangiopathy: a systematic review of published reports. *Blood* 2015;125:616–8.
35 Shibagaki Y, Fujita T. Thrombotic microangiopathy in malignant hypertension and hemolytic uremic syndrome (HUS)/ thrombotic thrombocytopenic Purpura (TTP): can we differentiate one from the other? *Hypertens Res* 2005;28:89–95.