OMCR

OMCR 2015 2 (4 pages)
doi:10.1093/omcr/omv001

Case Report

Thrombotic thrombocytopenic purpura with concomitant small- and large-vessel thrombosis, atypical posterior reversible encephalopathy syndrome and cerebral microbleeds

Wong Li Yu[1], Thomas Leung[2], Yannie Soo[2], Jessamyn Lee[2] and Ka Sing Wong[2,*]

[1]Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Shatin, Hong Kong and [2]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong

*Correspondence address. Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong. Tel: +852-26323493; Fax: +852-26323852; E-mail: ks-wong@cuhk.edu.hk

Received 3 October 2014; revised 6 December 2014; accepted 6 January 2015

We report a case of thrombotic thrombocytopenic purpura (TTP) with uncommon imaging features, namely concomitant small- and large-vessel thrombosis, atypical locations of posterior reversible encephalopathy syndrome (PRES) and microbleeds. A 58-year-old Chinese woman presented with slurred speech and multiple petechiae over lower limbs. Blood tests showed thrombocytopenia. Neuroimaging showed multiple acute small infarcts and PRES in the subcortical white matter, basal ganglia, thalamus, brainstem and occipital lobe. Microbleeds were noted. She was treated as TTP with infusion of cryo-reduced plasma (CRP). Patient subsequently developed dense right hemiplegia. Computed tomography of brain demonstrated a new major left middle cerebral artery territory infarct. She was stabilized after 2 weeks of treatment with daily CRP infusion, then received rehabilitation for major stroke. Early recognition of TTP provides the best chance of recovery as most lesions are reversible when TTP was treated. However, concurrent large artery thrombosis could cause major morbidity and mortality.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder characterized by a classic pentad—thrombocytopenia, haemolytic anaemia, neurological involvement, fever and renal impairment. Studies have established a relationship of TTP with deficiency of ADAMTS13, a circulating metalloprotease that cleaves plasma von Willebrand factor (vWF) [1, 2]. In the absence of ADAMTS13, vWF activated by a high level of shear stress in circulation would lead to vWF-platelet aggregation and thus microvascular thrombosis.

Neurological symptoms are frequently seen, and may mimic various conditions including stroke, seizure, acute delirium and coma. Approximately half of the patients at presentation and eventually 90% of them demonstrated neurological involvement [3]. Brain imaging in the acute stage often reveals abnormalities including posterior reversible encephalopathy syndrome (PRES), acute infarct and haemorrhage [4, 5]. PRES is the most commonly occurred abnormality, while acute infarcts and haemorrahges are less frequent [4]. TTP-associated stroke is usually small and involves multiple sites. Large artery thrombosis is a rare phenomenon which was only reported in a few patients in the literature [6–8]. Here we report a case of idiopathic TTP presented with concomitant small- and large-vessel thrombosis.

CASE REPORT

The patient was a 58-year-old Chinese woman with a history of hypertension, benzodiazepine dependence and dysthymia. She presented with slurring of speech and unsteady gait to the accident and emergency department, and was admitted as suspected stroke. On admission, she developed fever and confusion. Physical exam revealed a temperature of 38.3°C. No focal neurological signs were present. Multiple petechiae and purpura were seen over bilateral lower limbs. Complete blood count showed haemolytic anaemia and thrombocytopenia, with haemoglobin level 9.1 g/dl and platelet count 8×10^9/l. Blood film showed microangiopathic blood picture with

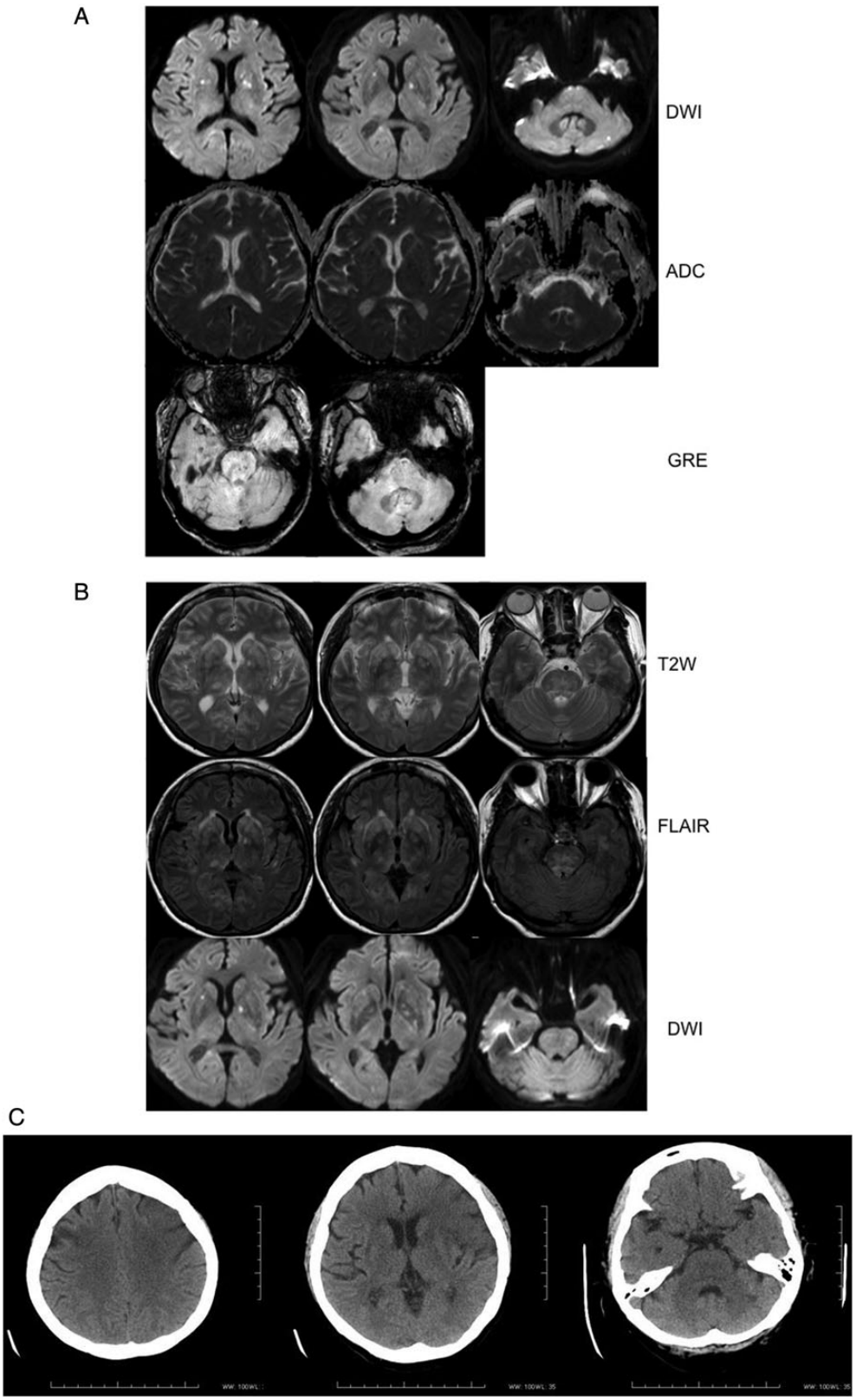

Figure 1: (**A**) Multiple punctate infarcts at bilateral basal ganglia, left thalamus and cerebellum with restricted diffusion on DWI and corresponding low signal on ADC map, suggesting acute infarcts. GRE showed multiple small dark dots indicating microbleeds in the brainstem and left cerebellar region. DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; GRE, Gradient-rated echo. (**B**) Symmetrical bilateral T2 and FLAIR hyperintensities in subcortical white matter, basal ganglia, thalamus, brainstem and occipital lobe, which show no corresponding restricted diffusion, indicating areas of cerebral oedema. Features are suggestive of posterior reversible leucoencephalopathy syndrome. FLAIR, fluid attenuated inversion recovery. (**C**) Plain CT brain showing multiple cortical and subcortical hypodensity over left MCA territory, indicating large artery thrombosis.

leucoerythroblastic blood picture. Lactate dehydrogenase (LDH) level was markedly elevated to 2799 u/l. D-dimer level was 6362 ng/ml. Renal function was normal. Toxicology screening was negative. Computed tomography (CT) of the brain on admission and lumbar puncture findings were unremarkable. Electroencephalogram was normal. Septic workup was unrevealing. Bone marrow aspirate demonstrated reactive changes without malignant infiltrate. She developed left upper limb weakness on Day 3 of admission. Serial CT brain revealed a small subarachnoid haemorrhage in the cerebral falx but no acute infarct. Follow-up CT scan was unremarkable. She was treated as TTP in view of her clinical picture, and infusion of cryo-reduced plasma (CRP) and intravenous antibiotics were started. Due to the lack of availability of ADAMTS13 assays in our laboratory, the test was not performed.

Magnetic resonance imaging of the brain was performed and showed multiple T2 and fluid attenuated inversion recovery (FLAIR) hyperintensities in the subcortical region, including bilateral basal ganglia, left thalamus and cerebellum. These areas showed high signal on diffusion-weighted imaging (DWI) with low signal on apparent diffusion coefficient (ADC) map in the corresponding regions suggesting acute infarcts (Fig. 1A). Symmetrical bilateral T2 and FLAIR hyperintensities in the subcortical white matter, basal ganglia, thalamus, brainstem and occipital lobe showed no corresponding restricted diffusion. These imaging features alone were nonspecific, however, in addition to the clinical condition of the patient, these changes were suggestive of PRES (Fig. 1B). Microbleeds were also noted in the brainstem and cerebellum (Fig. 1A). Magnetic resonance angiography was unremarkable.

Despite initial favourable response to CRP infusion, the patient subsequently developed dense right hemiplegia, right-sided neglect and aphasia. Urgent CT brain demonstrated multiple cortical and subcortical infarcts, including a major left middle cerebral artery territory infarct (Fig. 1C). Four cycles of plasma exchange were commenced but she remained unresponsive to the treatment. Trans-thoracic echocardiogram revealed no vegetations. One set of blood cultures grew enterococcus faecium, and she was treated with daptomycin and gentamicin. CT abdomen and pelvis was unremarkable. Plasma exchange was terminated in view of suboptimal response, and she was maintained with CRP infusion and antibiotics. Her clinical condition was further complicated by gastrointestinal bleeding caused by stress ulcer and gangrenous change of the toes accountable by the thrombotic phenomenon of TTP.

Her clinical condition stabilized after 2 weeks of treatment with daily CRP infusion. Platelet count recovered to normal level and LDH level dropped to 400. Patient then received rehabilitation care for her major stroke.

DISCUSSION

We report a case of TTP with uncommon imaging findings, namely large-vessel thrombosis, atypical locations of PRES and microbleeds. Stroke in TTP is often ischaemic with small infarcts [3]. Major stroke in TTP is uncommon but has been reported in a few patients. Our patient initially presented with punctate infarcts involving multiple areas, including the basal gangalia, thalamus and cerebellum. However, the disease became refractory to the treatment with CRP infusion and further thrombotic phenomenon occurred in the form of large artery thrombosis. Multiple cortical infarcts in the frontal lobe, cerebellum and left MCA territory were demonstrated on plain CT brain when patient developed dense right hemiplegia. As the baseline MRA was normal, we postulated that there was possible large thrombus formation in the heart and caused the cardio-embolic type of stroke in this patient.

Imaging features of PRES were also present in this patient in the occipital lobe, basal ganglia, thalamus and brainstem. PRES is a clinical syndrome of headache, altered mental states, seizure, and imaging findings of extensive bilateral white-matter abnormalities predominantly in the parieto-occipital region [9]. PRES is accountable by oedema in the posterior regions of the cerebral hemispheres. Involvement of the basal ganglia, thalamus and brainstem, as demonstrated in our patient, was reported as atypical features of PRES in TTP [10].

Cerebral microbleeds in TTP were reported in a patient presented with atypical PRES [10]. The mechanism was thought to be related to hyperperfusion causing destruction in the blood-brain barrier, as demonstrated by perfusion imaging in that case. However, there is only limited report on the occurrence of microbleeds in TTP and the significance of this finding remains uncertain.

TTP is a life-threatening multisystem disorder affecting major organs including brain, kidney and heart. Diffuse microthrombi formation in arterioles and capillaries leads to ischaemia in the end organs [1, 2]. Early recognition and prompt use of plasma exchange in TTP provide the best chance of recovery for patients. ADAMTS13 plasma level and its antibodies could be used as a diagnostic test for TTP [11]. However, as the assay may not be widely available, a high index of clinical suspicion would be important to establish a timely diagnosis. Most brain lesions shown on imaging could be reversible when the underlying TTP was treated [4]. However, large artery thrombosis could still occur in the course of disease, though rare and cause major morbidity and mortality in patients with TTP as in our patient.

REFERENCES

1. Tsai HM, Lian EC. Antibodies to von willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med* 1998; **339**:1585–94.
2. Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B, *et al.* Von willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med* 1998; **339**:1578–84.
3. Meloni G, Proia A, Antonini G, De Lena C, Guerrisi V, Capria S, *et al.* Thrombotic thrombocytopenic purpura: prospective neurologic, neuroimaging and neurophysiologic evaluation. *Haematologica* 2001; **86**:1194–9.

4. Burrus TM, Wijdicks EF, Rabinstein AA. Brain lesions are most often reversible in acute thrombotic thrombocytopenic purpura. *Neurology* 2009;**73**:66–70.
5. Bakshi R, Shaikh ZA, Bates VE, Kinkel PR. Thrombotic thrombocytopenic purpura: brain CT and MRI findings in 12 patients. *Neurology* 1999; **52**:1285–1288.
6. Scheid R, Hegenbart U, Ballaschke O, Von Cramon DY. Major stroke in thrombotic-thrombocytopenic purpura (moschcowitz syndrome). *Cerebrovasc Dis* 2004;**18**:83–5.
7. Aksay E, Kiyan S, Ersel M, Hudaverdi O. Thrombotic thrombocytopenic purpura mimicking acute ischemic stroke. *Emerg Med J* 2006;**23**:e51.
8. Kelly PJ, McDonald CT, Neill GO, Thomas C, Niles J, Rordorf G. Middle cerebral artery main stem thrombosis in two siblings with familial thrombotic thrombocytopenic purpura. *Neurology* 1998;**50**:1157–60.
9. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, *et al*. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996;**334**:494–500.
10. Bas DF, Oguz KK, Topcuoglu MA. Atypical reversible posterior leukoencephalopathy syndrome in thrombotic thrombocytopenic purpura. *Intern Med* 2008;**47**:1931–4.
11. Galbusera M, Noris M, Remuzzi G. Thrombotic thrombocytopenic purpura—then and now. *Semin Thromb Hemost* 2006;**32**:81–9.