

Atypical Reversible Posterior Leukoencephalopathy Syndrome in Thrombotic Thrombocytopenic Purpura

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Abstract

A 32-year-old man with an atypical form of reversible leukoencephalopathy syndrome (RPLS) caused by thrombotic thrombocytopenic purpura (TTP) is reported. In this particular case, a timely diagnosis of TTP was established primarily on the clinical findings, which led to the early initiation of plasmapheresis and resulted in excellent clinical recovery. The pathophysiological aspects of the relationship between TTP and RPLS are discussed in light of the clinical and radiological features (including diffusion- and perfusion-weighted magnetic resonance imaging studies) of this case. The mechanism for TTP-associated, or TTP-induced, leukoencephalopathy is suggested to be independent of hypertension and vasoconstriction. TTP-associated endothelial injury can play a major role as the inciting mechanism for the development of RPLS.

Key words: thrombotic thrombocytopenic purpura, microangiopathy, magnetic resonance imaging, leukoencephalopathy, stroke, perfusion, plasmapheresis

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is an autoimmune disorder characterized by a pentad consisting of thrombocytopenia, hemolytic anemia, renal dysfunction, neurological signs and fever. An assay to detect decreased activities of von Willebrand factor-cleaving protease, which is a disintegrin and metalloproteinase with thrombospondin type 1 motifs 13, (ADAMTS13) and anti-ADAMTS13 IgG antibodies in plasma are now being used to diagnose TTP (1). However, because this biomarker is not widely and readily available, familiarity with the clinic picture is still essential for the diagnosis and emergency initiation of the treatment (plasmapheresis).

As TTP is basically a disseminated thrombotic microangiopathy (2), one of the most commonly observed neurological involvements includes a variety of ischemic and hemorrhagic strokes (3). In addition to convulsion and encephalopathy without corresponding structural lesions perhaps due to systemic complications such as renal insufficiency and/or malignant hypertension, reversible posterior

leukoencephalopathy syndrome (RPLS) is another well-known and frequent central nervous system involvement pattern of TTP (3-6). We present herein a well-studied example of this association; TTP and RPLS, which offers an interesting opportunity to discuss and to shed light into the underlying mechanisms of neurological involvement in TTP, where documentation of cerebral perfusion abnormalities with MRI is scant (7).

Case Report

A previously healthy 32-year-old man was admitted because of a 10-day history of headache, diffuse abdominal pain, fever and progressive confusion. On admission, he was lethargic without any focal neurological deficits. His blood pressure was 110/50 mmHg. Physical examination was remarkable only for fever (peaked at 40.1°C). Laboratory studies showed erythrocyte sedimentation rate 80 mm/h, blood urea nitrogen 60.6 mg/dL, creatinine 1.87 mg/dL, hemoglobin 7.8 gr/dL, reticulocytes 8.29%, platelets 18,000/mm³, indirect bilirubin 2.95 (normal range, 0.2-1.2 mg/dL) and lactate dehydrogenase (LDH) 2778 (normal range, 230-460 U/

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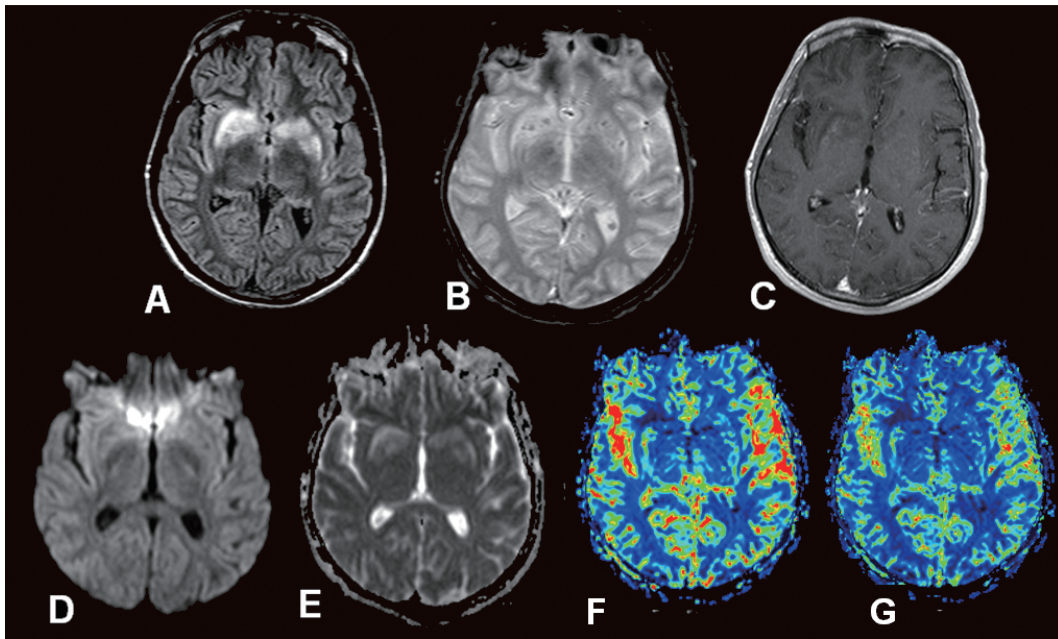


Figure 1. Bilateral basal ganglia and insular cortices are of increased intensity on FLAIR (A) with petechial hemorrhages on gradient echo T2*(B) imaging. Postcontrast T1W axial image shows faint enhancement in the basal ganglia and piamater (C). Trace image of DWI shows no signal change (D) with elevated values on ADC map (E) consistent with vasogenic edema. On CBV (F) and CBF (G) maps of perfusion weighted imaging, hyperemia is shown on insular cortices with a little reduction of these parameters in the right basal ganglia.

L). Direct and indirect Coombs' were negative. Prothrombin time, activated partial thromboplastin time, and activity of thrombin were within normal ranges. Generalized tonic-clonic seizure occurred twice in the emergency unit, and were treated with diazepam and levetiracetam. Following these seizures, his level of consciousness declined to coma, and left-sided weakness appeared. An emergency brain computed tomography was considered within normal limits at that time. Generalized slowing and voltage suppression was noted on the electroencephalography. Based on the presence of seizure, confusion, acute renal failure, hemolytic anemia and thrombocytopenia, the diagnosis of thrombotic thrombocytopenic purpura (TTP) was suggested, and plasma exchange was initiated at the 12th hour after admission, and continued on a daily basis afterward.

A cranial magnetic resonance (MR) imaging performed prior to the first plasma exchange revealed lesions with vasogenic edema (ADC value of basal ganglia lesions: 1.14×10^{-3} s/mm², ADC value of ipsilateral normal thalamus: 0.72×10^{-3} s/mm²) involving basal ganglia, insula and superior temporal gyri bilaterally. Scattered microhemorrhages along with faint contrast enhancement in the lesions and adjacent piamater were noted (Fig. 1A-E). A perfusion-weighted MR study (PWI), performed on the fifth day, disclosed increased cerebral blood volume (CBV) and cerebral blood flow (CBF) at insular and anterior temporal lobes bilaterally (Fig. 1F, G). On same day, cerebrospinal fluid (CSF) demonstrated no abnormality. Of note, immunoglobulin G index was 0.66, and oligoclonal band was absent. Thyroid func-

tion tests and antibodies, hepatic viral markers, anti-HIV, vasculitic markers, blood and CSF viral serology as well as cultures were negative or remained within normal limits. A computerized tomography (CT) angiography performed on the fourth day after admission showed normal intracranial and cervical vasculature.

Following the third plasma exchange, his neurological status improved progressively and dramatically. He became totally normal by the seventh day of admission. He had no further seizures. Hematological and renal abnormalities gradually recovered within two weeks. Along with plasma exchange, prednisolone 1 mg/kg per os was also administered on a daily basis.

In accordance with changes in clinical status, follow-up MR examinations, obtained on days 10 (Fig. 2A) and 20 (Fig. 2B), documented gradual resolution of the lesions along with contrast enhancement. Oral steroid was continued almost for 3 months, then tapered. One year later, his neurologic examination was normal.

Discussion

The neuroimaging features in the clinical setting of this patient are suggestive of atypical RPLS (8, 9). Typical and atypical RPLS share the same etiological and pathophysiological aspects (10). Features including involvement site other than posterior circulation, and cortices and subjacent white matter, the presence of contrast enhancement on post-gadolinium imaging, restricted diffusion, and irreversibility

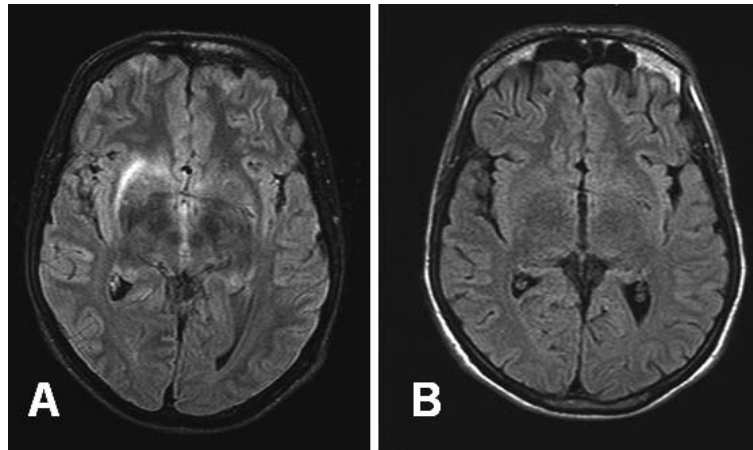


Figure 2. Partial and complete resolution of the lesions are seen on FLAIR images obtained at day-10 (A) and day-20 (B) respectively.

of the lesions are regarded as 'atypical' in this syndrome (10, 11). Basal ganglia, thalami, brainstem and deep white matter involvement may lead to extremely 'atypical' appearances on MR imaging and pose a diagnostic challenge especially in the absence of characteristic parieto-occipital lesions. Other less common manifestations were hemorrhage and a recently described unilateral variant (12). Generally, facilitated diffusion with elevated ADC values indicative of vasogenic edema is observed in RPLS. In the presence of additional hemorrhages, which are mainly petechial and perhaps represent another indicator of blood brain barrier break-down, in the edematous lesions, ADC values can be relatively decreased (13). However, restricted diffusion is another well-known atypical characteristic irrespective of hemorrhagic contamination, and does not rule out RPLS diagnosis, instead it may indicate irreversibility of the lesions (14). Cerebrovascular autoregulatory dysfunction is considered as the dominant underlying mechanism of these lesions. PWI in the present case showed an increase in both CBF and CBV indicating that the hyperperfusion most likely resulted from disordered cerebral autoregulation. This is a previously recognized but rarely illustrated finding in RPLS cases (9, 14). Most of the TTP-associated RPLS patients have difficult-to-control hypertension and/or renal failure indicating a connection between RPLS and hypertensive encephalopathy (3). TTP-induced RPLS infrequently results from cerebral reversible segmental vasoconstriction syndrome (4). However, the presented case demonstrates that hypertension and vasoconstriction may not be necessary prerequisites to RPLS in TTP, perhaps similar to the other situations associated with RPLS (10, 12). Multifactorial mechanisms including toxicity-related blood-brain barrier injury and widespread endothelial injury may play a role (7). In

this context, an atypical location of RPLS lesions may be related to the regional, such as basal ganglia, white matter and fibers running in the white matter, circulatory dynamics.

Together with or without RPLS, cerebral infarctions and hemorrhages are the other most frequently observed form of neurological involvement in patients with TTP (3). TTP-related ischemic strokes can be classified into four groups as small and usually multiple cortically-located infarctions, lacunes, watershed infarcts and large territorial strokes caused by occlusion of a major basal cerebral artery. Stroke in TTP is caused by thrombotic microangiopathy in which arteriolar and capillary endothelial damage result in diffuse microthrombi formation in the microcirculation leading to hypoperfusion. Microangiopathic cerebral infarctions are prone to hemorrhagic transformation. Thrombocytopenia and hypertension play a role in the occurrence of not only hemorrhagic transformation but also primary intracerebral hematoma in TTP. As demonstrated by MR perfusion studies in this case report, hyperperfusion can be linked to the development of cerebral (micro) hemorrhages in TTP. Hyperperfusion-related destruction of the blood brain barrier, which is evident from the presence of contrast enhancement in the present case, can be another factor.

Once again, this case underlines the importance of the timely diagnosis and treatment of patients with TTP. As mentioned before, demonstration of the plasma level of ADAMTS-13, and its antibodies are diagnostic in TTP (1), but, before the general availability of rapid and reliable assays, it is not realistic to wait for the test results in emergency cases. The presence of the classical pentad of clinical findings, known also as Moschowitz's criteria named after his first description of the syndrome, should be considered sufficient to initiate plasma exchange.

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