

## Brief Communication

# Unseen face of varicella-zoster infection in adults

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### Abstract

Varicella infection is common in children caused by varicella-zoster virus (VZV). VZV is known to cause cerebral arterial vasculopathy and antibody-mediated hypercoagulable state leading to thrombotic complications in children. Such complications in adults are very rare. We report three cases that represent the unseen face of primary varicella infection in adults. Simultaneous involvement of cortical venous sinus thrombosis and deep vein thrombosis leading to clot in right atrium and pulmonary embolism in first case; cortical venous sinus thrombosis in second case; and deep vein thrombosis in third case. Early diagnosis and management can help prevent associated morbidity and mortality.

**Keywords:** Acquired protein-S deficiency, cortical venous sinus thrombosis, deep vein thrombosis, hypercoagulability, pulmonary embolism, varicella-zoster infection

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## Introduction

Varicella-zoster virus (VZV) infection occurs as an acute viral exanthematous illness in children and is typically benign. However, VZV infection in adults is known to be more severe and associated with increased morbidity. Due to the systemic nature of varicella, it can involve any organ system, but the incidence of neurological complications is reported to be <1%.<sup>[1]</sup> The neurological manifestations vary from benign cerebellitis to malignant central nervous system vasculitis, with zoster emerging as an important risk factor for stroke. Stroke due to arterial vasculitis is well known but cerebral venous sinus thrombosis following varicella infection is rarely reported. Here, we have a series of three adult male patients presenting with cortical venous thrombosis (CVT), deep venous thrombosis, and other thromboembolic sequelae due to hypercoagulable state following varicella-zoster infection. This series provides insight into the unseen faces of varicella infection in adult humans.

## Case Reports

### Case 1

A 37-year-old right-handed male presented with a history of left focal motor seizures (3–4 episodes), involving the face and left arm, with preserved consciousness. There was associated history of diffuse non-localizing headache of moderate intensity. He had no history of fever, ear discharge, previous seizures, or any drug addiction. He had no significant medical or surgical illness in the past. Three weeks prior there was a history of fever with maculopapular centripetal rash for which he had received oral acyclovir for 14 days, suggesting the diagnosis of varicella infection. On examination, the patient was conscious (Glasgow coma scale-15) with intact comprehension. Systemic examination revealed residual scars with scrubs, mainly on the trunk and face. Motor system examination

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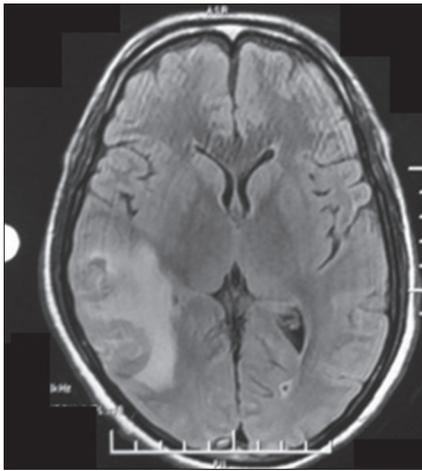
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revealed left hemiparesis (power 4/5 MRC) with left extensor planter response. Sensory system was normal with no meningeal signs. Laboratory investigations were within range except erythrocyte sedimentation rate of 65 mm. Magnetic resonance (MR) brain imaging showed right frontoparietal venous infarction [Figure 1] and on MR venography, there was thrombosis of superior sagittal, right transverse and sigmoid sinus [Figure 2]. He was started on unfractionated heparin infusion and antiepileptics. He remained stable till the 5<sup>th</sup> day, when he suddenly developed breathlessness and chest pain. Electrocardiogram revealed sinus tachycardia (130/min) with T-wave inversion in anterior chest leads. He was hemodynamically stable with normal creatine phosphokinase-MB and Trop-T but slightly elevated B-type natriuretic peptide (570 pg/dl). Transthoracic echocardiography revealed dilated RA and right ventricular with mobile mass in the right



**Figure 1:** Magnetic resonance imaging brain showing large area of altered signal intensity in frontoparietal area on fluid attenuation inversion recovery image, suggestive of venous thrombosis

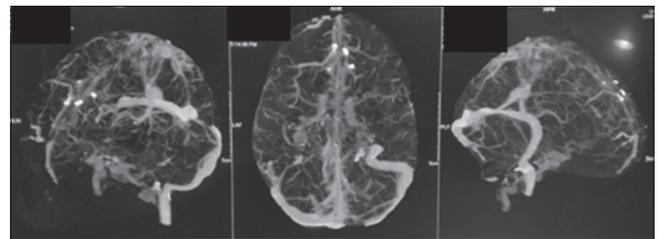


**Figure 3:** Computer tomography imaging of the chest (transverse section) showing bilateral cutoff sign in the main pulmonary arteries suggestive of pulmonary embolism

atrium (RA) [Video 1] necessitating immediate computed tomography (CT) chest with pulmonary angiography. It revealed left lower zone consolidation with bilateral pulmonary artery thrombosis [Figure 3]. Venous Doppler of lower limbs revealed thrombosis of the left femoral and distal popliteal vein. The patient was continued on heparin infusion followed by oral anticoagulation. He gradually improved and was discharged on day 12 with no neurological sequel. At 3 months follow-up, his magnetic resonance spectroscopy was 1 and echocardiography also showed resolution of the atrial thrombus.

### Case 2

A 30-year-old nonsmoker, right-handed male, presented with continuous diffuse headache for 10 days and left side weakness of 3 days duration. The illness started with fever and maculopapular rash predominantly on the trunk and limbs about 3 weeks back. The lesions were centripetal in distribution confirming the diagnosis to be varicella. They were in crusting stage when he developed neurological complaints. He had no history of seizures. On examination, he was drowsy but arousable. General physical examination and vitals were normal except postvaricella scar marks [Figure 4]. Neurological examination revealed normal cranial nerves, bilateral papilledema (grade 2), left-sided



**Figure 2:** Magnetic resonance venography showing lack of flow in superior sagittal sinus, left transverse sinus suggestive of cortical venous sinus thrombosis



**Figure 4:** Maculopapular skin lesions following varicella-zoster infection, in healing stage

hemiparesis; power 4/5 in upper and 3/5 in lower limb. Routine hemogram and serum biochemistry were normal. A plain CT scan showed a hemorrhagic infarct in the right temporoparietal lobe with edema and mass effect. The findings, examination, and investigations were suggestive of cortical venous sinus thrombosis and MR venography revealed loss of normal signal intensity in transverse sinus and sigmoid sinus on the right side [Figure 5]. The patient was started on antiedema measures and injection low molecular weight heparin, followed by oral anticoagulation. His neurological symptoms improved gradually over next 3 weeks. The patient was discharged on oral anticoagulants.

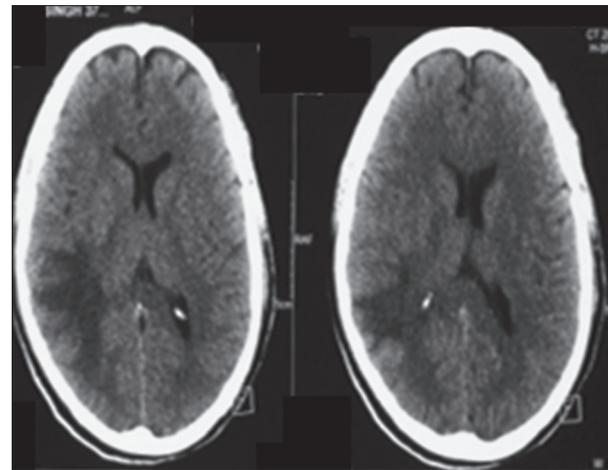
**Case 3**

A 33-year-old teetotaler male presented with a history of pain and swelling in the left lower limb. On examination, he had swelling and tenderness in the left calf. He had no history of trauma or prolonged immobilization but history suggestive of varicella infection 2 weeks prior. On local examination, there was tenderness and swelling present in the left calf. Systemic examination was normal. Laboratory investigations including hemogram, biochemistry, and ultrasonography abdomen were normal. Doppler of lower limbs revealed thrombosis of left popliteal vein. He was started on heparin which was overlapped with oral anticoagulation and pain and tenderness gradually disappeared. After 2 months, he was asymptomatic and had occasional swelling of left leg after walking for long distance.

All the patients were positive for varicella IgM antibodies. Serology for human immunodeficiency virus, hepatitis-B surface antigen, vasculitis, connective tissue disorders (antinuclear antibodies, anticardiolipin antibodies), and serum antiphospholipid antibodies was negative. Investigation for procoagulant states such as protein-c, protein-s, factor-V, antithrombin-III, and homocysteine levels was within normal limits in Case 1 and 3, but protein-S was significantly low in Case 2.

**Discussion**

Varicella infection commonly presents as self-limiting skin manifestations in children. Postviral thromboembolism resulting in cerebral venous thrombosis, deep vein thrombosis, or pulmonary embolism is a rare presentation even in children. Literature has evidence of only a few isolated cases of thrombosis of either cortical venous sinus or deep veins of the lower limbs in adults [Table 1]; however, this is the first case in literature to report the occurrence of extensive thrombosis simultaneously involving the cortical venous



**Figure 5:** Noncontrast computed tomography suggestive of the right parietotemporal venous infarction, with mass effect

**Table 1: Reported cases of hypercoagulability complications following varicella-zoster infection**

Author	Year	No of patients	Age (years)	Sex	Clinical presentation
Siddiqi et al. <sup>[2]</sup>	2012	2 (1 child, 1 adult)	20	M	CVST with coexistent middle cerebral artery involvement.
Sardana V et al. <sup>[4]</sup>	2012	1	30	M	CVST
Sada S et al. <sup>[6]</sup>	2012	1	30	M	CVST
Menon B, Goyal R <sup>[7]</sup>	2012	1	33	M	CVST
Sudhaker B et al. <sup>[8]</sup>	2014	1	26	M	CVST
Our Series	2016	3 adults	37	M	CVST, deep vein thrombosis, pulmonary embolism with clot in Right atrium
			30	M	CVST
			33	M	DVT

CVST: Cerebral venous sinus thrombosis; DVT: Deep vein thrombosis

sinus, deep veins of the leg, and atrial thrombus with pulmonary embolism following varicella infection. The other distinguishing feature was involvement of male gender though previous literature suggests that 75% of adult patients with CVT are females.<sup>[2]</sup>

The history, skin lesions, and positive viral antibodies support the diagnosis of varicella infection in all the cases. Varicella as the causative factor of neurological manifestations is also evidenced by the temporal association between the development of skin lesions and thrombotic complications. The latent period of 2–3 weeks signifies the time for the direct venous endothelium damage or development of autoantibodies to natural anticoagulants leading to widespread thrombotic process as in our first case. VZV is the only human virus that has been proven to replicate in cerebral arteries. Studies on pathogenesis reveal that upon reactivation, VZV travels transaxonally to the adventitia of arteries, followed by transmural migration

to the arterial media and intima, pathological vascular remodeling, leading to stroke.<sup>[3]</sup> The exact mechanism of pathogenesis of venous thrombosis following varicella is not known as for arteriopathy but the postulated theories are vasculitis, direct endothelial damage, or acquired protein S deficiency secondary to molecular mimicry.<sup>[4]</sup>

Our patients were extensively evaluated for hypercoagulable states and only case 2 had protein S deficiency. Josephson *et al.* in a cross-sectional study done on 95 children showed that 43 children had antiphospholipid antibodies and some had a significant reduction in protein-S levels postvaricella infection, describing it as varicella autoantibody syndrome.<sup>[5]</sup> These induced autoantibodies to protein-S could lead to acquired protein-S deficiency and produce a hypercoagulable state causing venous sinus thrombosis as in our case 2.

## Conclusion

Our cases demonstrate that physician should have high index of suspicion for hypercoagulability in patients following varicella infection as the clinical course could be complicated by widespread thrombosis and embolic phenomenon which can be life-threatening. Early institution of treatment with anticoagulation and

adequate hydration cannot only reduce mortality but also result in better outcome.

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## Conflicts of interest

There are no conflicts of interest.

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