Reactivated Varicella Zoster Virus May Cause Peripheral Arterial Thrombosis

To the Editor:

The varicella zoster virus (VZV) is a double-stranded DNA virus of the *Herpesviridae* family. The virus, which causes chicken pox, primarily infects children. Generally, after the infection, the virus becomes latent in ganglionic neurons along the entire neuroaxis. In particular cases, years after the infection, the reactivation of the VZV can cause zoster (shingles).

A 71-year-old man had arterial thrombosis after a herpes zoster infection. For 5 years prior to hospital admission, he had been receiving treatment for recurrent episcleritis and temporal arteritis. His first admission was because of numbness in his left hand. Two weeks before admission, he had been diagnosed with a herpes zoster eruption in his left upper extremity matching with the C6 dermatome. When his symptoms began, he was taking 20 mg/day leflunomide and 7.5 mg/day prednisolone. At his first examination, he had no pulse in his left radial artery. Double subtraction angiography of the left upper extremity showed the proximal left radial artery was thin-caliber and occluded (Figure 1). His left hand was supplied from the palmar arch, which included the ulnar artery (Figure 2). The hemogram and blood biochemistry were normal. Further, he had factor V Leiden heterozygosity, while the prothrombin and *MTHFR* genes were normal. The activity of protein C, protein S, and antithrombin were within normal levels, at 72% (normal 70%–130%), 93% (65%–140%), and 84% (80%–120%), respectively. While the protein C resistance was measured as normal at 0.6 (normal < 0.86), both the prothrombin time and the activated partial thromboplastin time were also normal. Moreover, the erythrocyte sedimentation rate was 40 mm/h and C-reactive protein level 33.6 mg/l. The antinuclear antibody, antiphospholipid antibodies (aPL), and lupus anticoagulant (LAC) were all negative. After the diagnosis, he began acyclovir and systemic intravenous unfractionated heparin. Six months after starting the treatment, his symptoms were nearly resolved.

The patient is among the first to have a disease with a possible link between the reactivation of the VZV and arterial thrombosis. The localization of the herpes zoster eruption and the thrombosis were the same.

There are only 5 reported cases of adults having arterial thrombotic complications of the VZV, including our patient. All the patients had primary varicella zoster infection, and the thrombosis of the lower extremity arteries was far from the primary location of the infection. One patient was immunocompromised by having taken cyclosporine. Since the immunofluorescence performed on the vessel biopsy showed C3 deposits, the authors concluded that the thrombosis was due to vasculitis secondary to VZV infection[1]. The other 3 reported cases of thrombosis had deficiencies in free



Figure 2. The left hand was supplied from the palmar arch, including the ulnar artery.

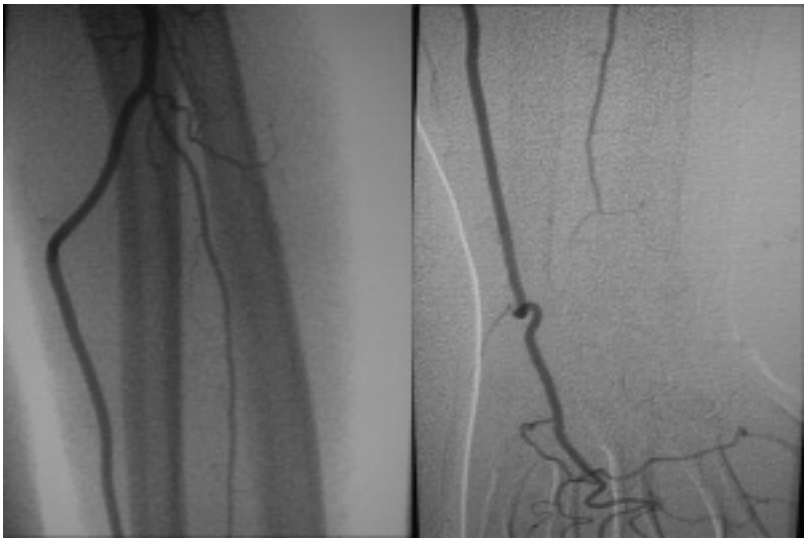


Figure 1. Double subtraction angiography shows that the proximal left radial artery was thin-caliber and occluded.

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protein S[2,3]. Among these cases, 2 patients were also found to have aPL and the other had LAC. However, the fifth patient had no risk factor for thrombosis[4].

There are 3 main explanations for the relationship between the viral infections and thrombosis: transient emergence of the antiphospolipid antibodies[5], vasculitis[6], and atherosclerosis[7]. In this context, 2 phenomena seem relevant to atherosclerosis.

Vascular thrombosis may occur due to thrombophilia after varicella infection. An example is a 16-year-old boy who had acute right iliofemoro-popliteal deep vein thrombosis (DVT). On admission, the IgM and the IgG anticardiolipin antibodies were both positive. The IgM anticardiolipin antibodies remained positive 6 weeks later, suggesting their role as a predisposing factor for DVT[8]. In a study[9] investigating the cause of purpura fulminans, disseminated intravascular coagulation, or thrombosis in 7 children with varicella, the thrombosis was associated with the presence of aPL in varicella infections. Moreover, the investigators found that all the children had LAC and protein S deficiency. In addition, 4 of those patients had antiphospolipid or anticardiolipin antibodies[9]. In another study, 2 men had varicella pneumonia and profound lower extremity ischemia caused by thrombosis of the profunda femoris and the tibial arteries. Both patients had free protein S deficiency. The IgG and the IgM aPL were present in 1 of the patients, while there was evidence that the other had the LAC[2].

Vasculitis occasionally develops after varicella virus infection in the form of a central neurological deficiency involving the retina or more rarely the skin or kidneys[6]. The herpes virus was recovered from human brain cells and the trigeminal ganglion cells. The trigeminal nerve innervates the proximal middle cerebral and posterior cerebral arteries, and most likely transmits the virus directly to the vessel. A delayed vasculopathy may also be due to an autoimmune phenomenon induced by circulating immune complexes[10].

For our patient, there was no thrombophilic factor, including antiphospholid antibodies. The time between the thrombosis and the infection was not long enough for the thrombosis to be caused by the atherosclerosis, and except for the radial artery, there was no pathology in the aorta or the first branches of the aorta. Moreover, the localization of the arterial thrombosis was the same as the herpes zoster eruption. Hence, we believe that the most probable pathogenesis of the thrombosis is vasculitis due to direct transmission of the virus, which might have come from the nerves originating from the plexus brachialis, which innervates the radial artery. To our knowledge, our patient is the first case to develop peripheral arterial thrombosis possibly due to direct transmission of the varicella zoster virus from the nerves outside the central nervous system.

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