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Case Report

Hidden Deep Vein Thrombosis Behind Unilateral Lower Extremity Herpes Zoster Infection

Meity Ardiana[1*], MD; Inna Maya Sufiyah[1], MD; Safira Rahma[2], MD

ABSTRACT

Deep vein thrombosis (DVT) occurs most commonly in the lower extremities and is related to the Virchow triad. While reactivation of the *varicella-zoster* virus (VZV) is rare when it occurs in the lower extremity dermatome, we present and discuss herpes zoster infection in immunocompromised individuals, which has similar manifestations yet can lead to unexpected, serious, life-threatening DVT complications. A 52-year-old woman with overweight and diabetes mellitus presented to the emergency department with 3 days of fever and a sudden, painful, swollen left leg. There was no history of chickenpox, trauma, surgery, or immobilization. She was using insulin glulisine and glargine. The physical examination was normal, except for a skin eruption characterized by a vesicle-pustule-blister group that followed the L4–L5 dermatome. Laboratory tests revealed leukocytosis and increased D-dimer levels. A duplex ultrasound was performed, which showed a thrombotic filling defect in the left common femoral vein and DVT in the left leg. The patient was treated with oral acyclovir, subcutaneous injection of fondaparinux, insulin glargine, and glulisine. Her symptoms improved within 7 days during her inpatient stay. After discharge, a follow-up duplex ultrasound evaluation revealed a reduced thrombus in the left common femoral vein. This case highlights that VZV reactivation in immunocompromised individuals can be complicated by DVT. It requires heightened clinical awareness of herpes zoster and related complications with similar manifestations, to provide precise and prompt treatment, and prevent worse outcomes. ***(Iranian Heart Journal 2024; 25(4): 111-116)***

KEYWORDS: Varicella zoster virus, Herpes zoster, Deep vein thrombosis, Immunocompromised, Lower extremity

[1] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[2] Dr Iskak General Hospital, Tulungagung, Indonesia.

*** Corresponding Author:** Meity Ardiana, MD; Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
Email: meityardiana@fk.unair.ac.id **Tel:** +6281259808492

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Deep vein thrombosis (DVT) in the lower extremity occurs more commonly than thrombus formation in superficial veins. [1] Although DVT often occurs in the calves, it may also develop in the proximal veins such as the popliteal, femoral, and iliac veins. Some conditions that can predispose individuals to DVT are related to the 3 factors of the Virchow triad, [1, 2] which include inherited or acquired risk factors. [1] The clinical presentation of DVT may be asymptomatic or symptomatic, with discomfort and swelling in the affected extremities. [1, 2] *Varicella zoster*, a double-stranded DNA virus, can become latent in a ganglion after primary infection, resulting in

herpes zoster (shingles). [3] There have been only 8 reported cases of herpes zoster associated with cardiovascular disease worldwide, with 60% of the cases being female and an average age of 58 years. Most herpes zoster infections involve the chest, body, and facial regions, but they rarely localize to the extremity dermatome. [4]

Cardiovascular disease comorbidities such as hypertension, diabetes mellitus, and dyslipidemia can impair cellular immunity. [5] Immunocompromised individuals, including those with cardiovascular comorbidities, are at high risk (50%) of *varicella-zoster* virus (VZV) reactivation, which can lead to atypical clinical manifestations or complications. [6] Diabetes mellitus, in particular, has been shown to significantly increase the risk of developing herpes zoster infections by 1.6-fold. [5]

Here, we present a case of VZV reactivation infection in the lower extremities of an immunocompromised individual, leading to serious cardiovascular complications as a rare case.

Case Report

A 52-year-old woman with overweight and diabetes mellitus presented to the emergency department with a 3-day history of pain, burning, and swelling in her left lower extremity accompanied by fever. Sudden rashes and spreading blisters developed on her left lower extremity for 2 days. After 2 days of inpatient care, her burning sensation decreased, but the pain persisted at the same level. She reported no dyspnea, cough, or dizziness. There was no reported history of VZV infection or chickenpox. The patient was receiving oral valacyclovir (1000 mg 3 times daily), along with subcutaneous insulin administration of glulisine (8 IU 3 times daily) and glargine (16 IU) at night. No history of trauma, surgery, or immobilization was noted.

The physical examination was largely unremarkable, except for findings related to the left lower extremity. These findings included edema, a shiny appearance, and severe tenderness. Skin eruptions, heterogenous vesicle-pustule groups, and blisters localized to the L4-L5 dermatome were also observed on the left lower extremity (Fig. 1A). The ECG showed sinus rhythm at 100 bpm, and the chest X-ray revealed cardiomegaly. Laboratory findings were largely within normal limits, except for an elevated leukocyte count of 11.89 × 109/L and plasma glucose levels. On the first day, plasma glucose was 449 mg/dL but subsequently decreased to 66 mg/dL, with a 2-hour postprandial blood glucose level of 153 mg/dL when the patient was referred to our care. A duplex ultrasound was performed, which identified a thrombotic filling defect in the left lower extremity at the left common femoral vein, indicative of DVT (Fig. 2). Additionally, an elevated D-Dimer level (> 10000 ng/mL) was observed.

The patient was administered additional medications, including a subcutaneous injection of fondaparinux (75 mg once daily) for 5 days, oral atorvastatin (40 mg), and clopidogrel (75 mg once daily). Following 7 days of treatment, the patient showed improvement with no symptoms and was discharged as an outpatient (Fig. 1B). She was advised to continue clopidogrel (75 mg once daily) and valacyclovir (1000 mg 3 times daily). Additionally, the anticoagulant regimen was changed to rivaroxaban (15 mg twice daily). A subsequent duplex ultrasound demonstrated reduced thrombus (Fig. 3).

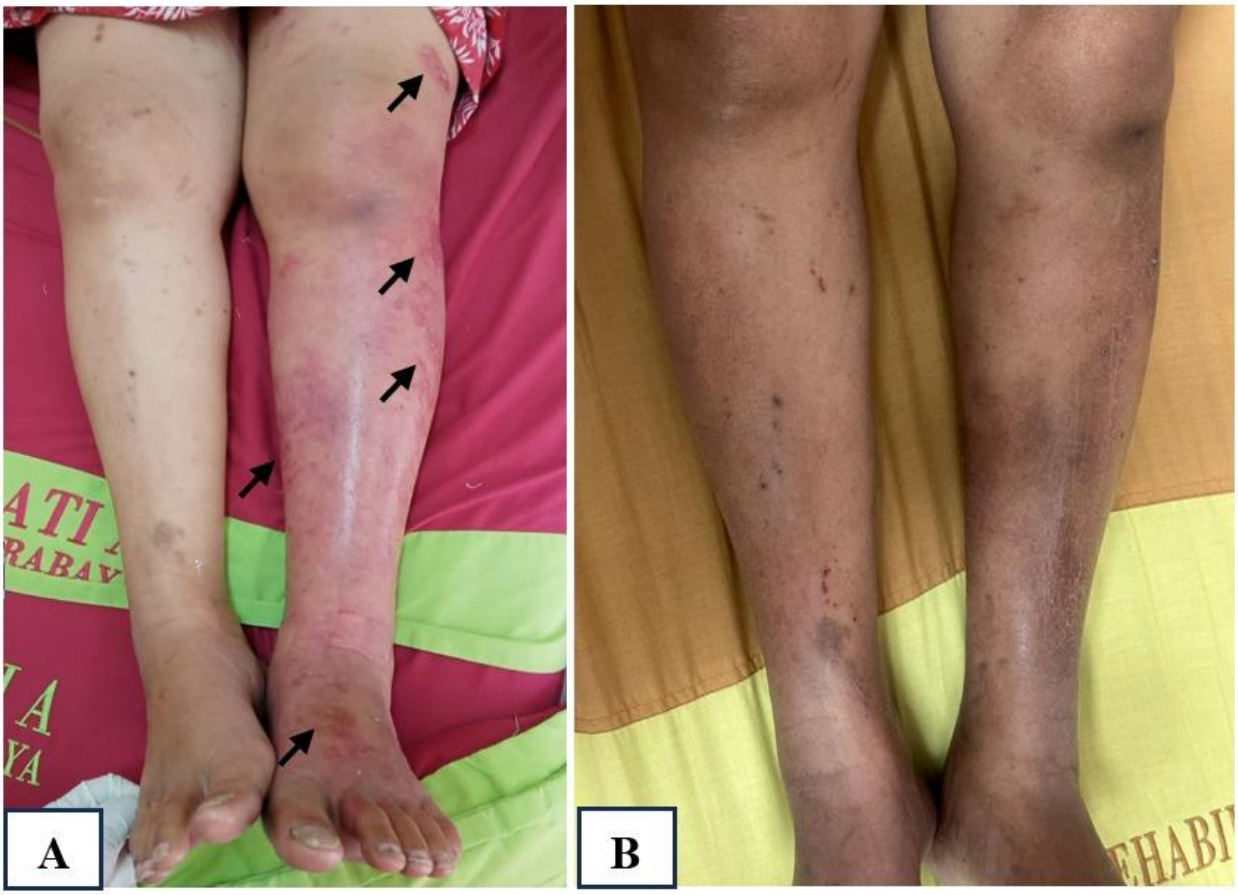

Figure 1: The images illustrate A) the skin presentation of herpes zoster following the L4-L5 dermatome (black arrow) and B) the improvement in the skin presentation after 7 days of inpatient care.

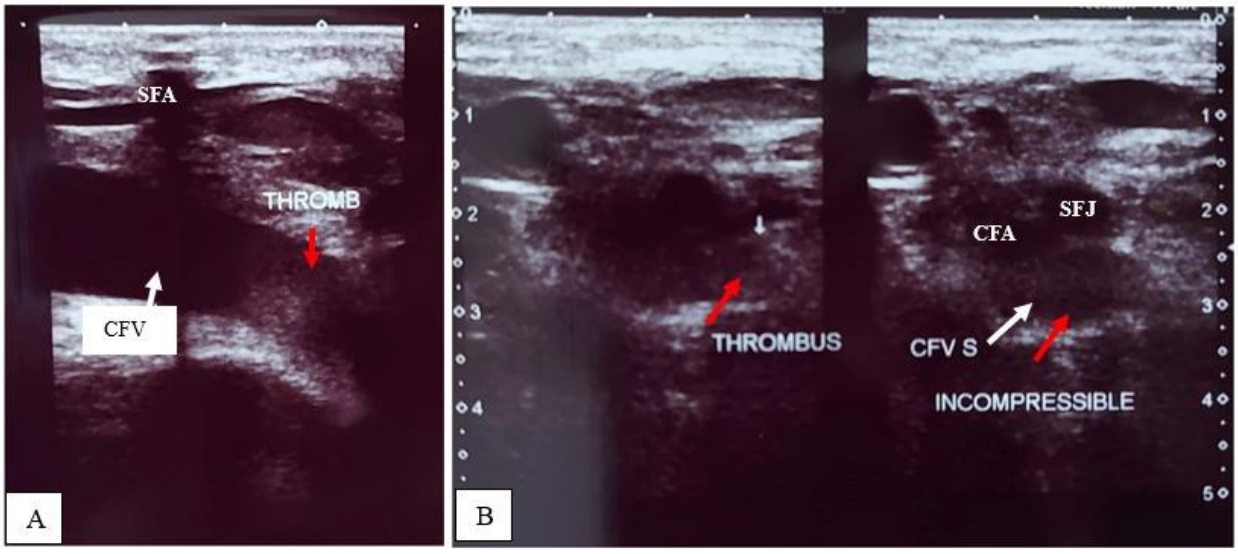

Figure 2: The patient's vascular duplex ultrasonography demonstrates a thrombotic filling defect, characterized by an incompressible thrombus (red arrow), along the left lower extremity vein at the left common femoral vein (CFV) with high venous flow (+). This is depicted in both the longitudinal view (A) and the transverse view (B).

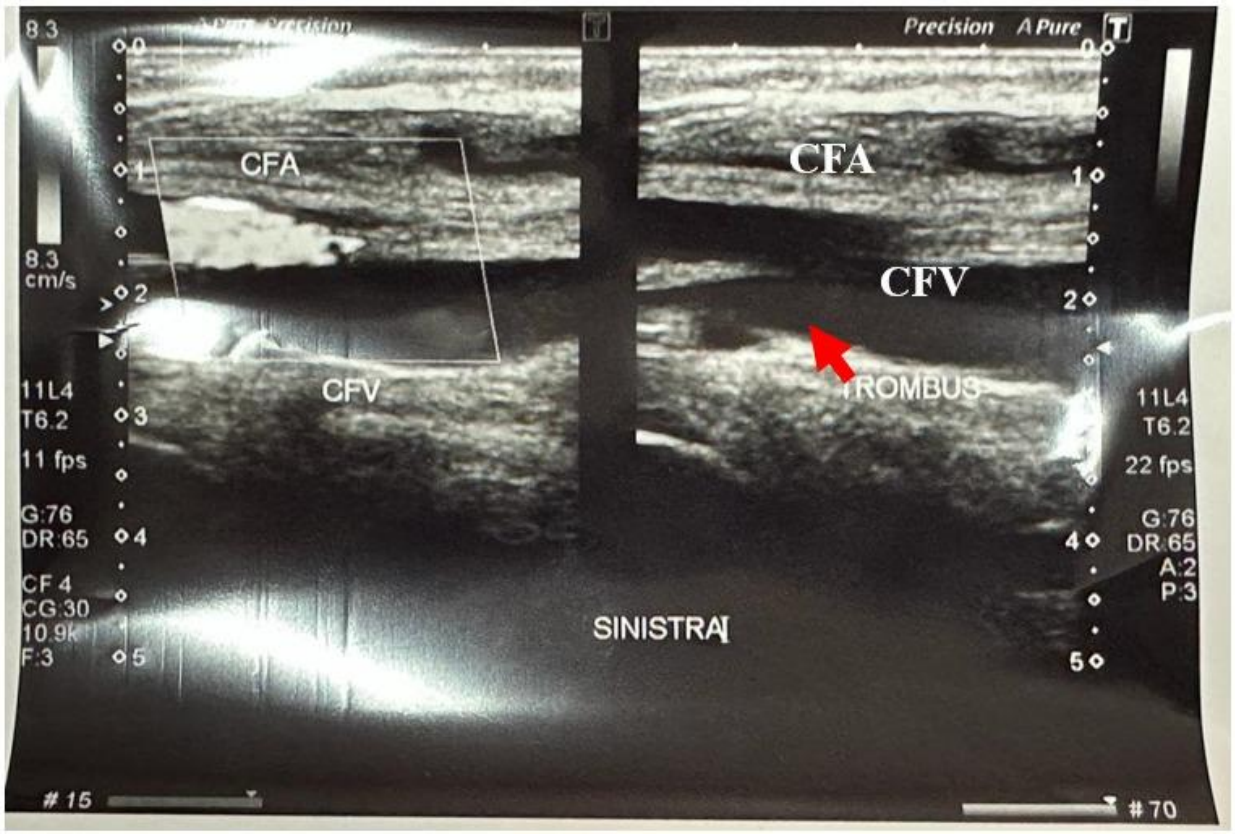

Figure 3: The patient's vascular duplex ultrasonography shows a reduced thrombus (red arrow) at the left common femoral vein (CFV).

DISCUSSION

Immunocompromised individuals with cardiovascular risk factors, such as diabetes mellitus, hypertension, and dyslipidemia, often experience cellular immunity impairment, which contributes to an increased risk of cardiovascular disease. [3] Research conducted by Qin et al [7] suggested that diabetes mellitus was associated with reduced endogenous fibrinolysis, elevated procoagulant factor levels, and endothelial damage, further highlighting the connection between diabetes and increased cardiovascular risk.

VZV reactivation, known as herpes zoster, typically occurs when the immune system is weakened, with a higher incidence among older adults. [4] Furthermore, VZV has been associated with arterial vasculopathy, [1] which may contribute to endothelial damage in blood vessels. [8] Previous research has indicated that varicella infection can lead to thrombosis through the production of antiphospholipid antibodies and direct infection of blood vessels. This connection was further supported by the discovery of VZV DNA in the cerebrospinal fluid during an autopsy study of a patient who passed away due to intracranial VZV-related vasculopathy. [9] Herpes zoster infection has been shown to spread both locally and centrally, potentially infecting cerebral and extracranial arteries and causing vasculopathy. This can result in various complications, including ischemic stroke, aneurysm, cavernous sinus thrombosis, giant cell arteritis, granulomatous aortitis, and increased risk of cardiovascular diseases such as atrial fibrillation and ischemia. [3] Consequently, the female patient in this case study, who had comorbidities of overweight

and diabetes mellitus, may be more susceptible to VZV reactivation, thereby increasing her likelihood of developing DVT. DVT has been identified as a rare complication of herpes zoster infection. [8] The local inflammatory response triggered by herpes zoster can result in vessel occlusion and subsequent ischemia, characterized by internal elastic lamina rupture, intimal hyperplasia, and a decrease in smooth muscle cells within the medial layer. [3] This evidence bolsters the concept of VZV invasion-induced thrombosis, with the thrombotic site typically occurring in the same location as the infection. [9]

A limited number of studies have reported cases of herpes zoster infection with DVT in the lower extremity, mirroring the present case. One such case involves an immunocompetent patient who experienced herpes zoster following the L5 dermatome and was diagnosed with DVT on the fifth day of hospitalization using computed tomography venography. The patient received a subcutaneous low-molecular-weight heparin injection for 5 days, followed by a switch to oral warfarin on the 10th day of hospitalization after DVT resolution was confirmed. [10] The second case involved a 19-year-old male patient with a history of VZV infection 10 days before hospital admission. In this instance, DVT was detected after 4 days of inpatient care. Further investigation revealed active protein C resistance and factor V Leiden mutation as contributing factors to thrombosis. The patient was discharged following anticoagulant therapy. [11]

In the present case, a diabetes mellitus patient with herpes zoster infection was diagnosed with DVT within 2 days of hospital admission. Although diabetes mellitus has not been directly linked to DVT, pulmonary embolism, venous thrombosis embolism, and a higher body mass index (BMI) have been shown to have a significant correlation with the development of these conditions. [12] Nevertheless, diabetes mellitus is recognized to contribute to endothelial damage and create an immunocompromised state, which, in conjunction with a higher BMI, can exacerbate herpes zoster infection-induced thrombosis. [7] Consequently, the combination of herpes zoster infection and obesity may have further heightened the severity of DVT incidence in this case.

In summary, this case presents a female patient with complex clinical manifestations that posed challenges in reaching an accurate diagnosis. The symptoms of swelling and leg discomfort could be indicative of various conditions, such as DVT, cellulitis, or abscess, in addition to herpes zoster. As a result, timely and accurate diagnosis is crucial in ensuring the administration of appropriate treatment. Hence, in addition to administering anticoagulants and managing cardiovascular disease risk factors, effective treatment of herpes zoster plays a significant role in minimizing the cumulative risk of thrombosis. A multidisciplinary approach is essential in addressing the various aspects of this complex clinical scenario.

CONCLUSIONS

Our case report highlights the rare occurrence of herpes zoster infection in the lower extremity, leading to the development of DVT in an immunocompromised patient. It emphasizes the susceptibility of immunocompromised individuals with herpes zoster infection to concurrent DVT, posing diagnostic challenges due to the similarity in presenting symptoms. Accurate and timely diagnosis is crucial in administering appropriate treatment and preventing further complications.

Study Limitations

Our study is subject to a few limitations. We did not have information regarding the patient's usage of oral contraceptives, which

is a known risk factor for DVT. Additionally, her insurance coverage posed constraints on the laboratory tests that could be performed in our country. As a result, blood gas analysis was not conducted, despite the patient presenting with hyperglycemia initially, due to normal physical examination findings.

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Conflict of Interest
The authors declare that they have no potential conflicts of interest to disclose.

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