Radiology Case Reports 19 (2024) 3244–3249

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/radcr

Case Report

Isolated cortical vein thrombosis with hemorrhagic infarction during the application of a transdermal estradiol patch: A case report ☆,☆☆

*Haruki Hirata, MD**, *Yuta Kaneshiro, MD*, *Yumiko Urano, MD*, *Keiji Murata, MD, PhD*

Department of Neurosurgery, Shimada General Medical Center, 1200-5 Noda, Shimada City, Shizuoka, Japan

ARTICLE INFO

Article history:
Received 6 March 2024
Accepted 20 April 2024

Keywords:
Isolated cortical vein thrombosis
Brain hemorrhage
Transdermal estradiol patch

ABSTRACT

Isolated cortical vein thrombosis (ICVT) is a rarer subtype of cerebral venous sinus thrombosis (CVST) that involves only the cortical veins without any thrombosis in the major cerebral veins or sinuses. Among the known causes of CVST are factors, such as being a young female or the use of hormonal preparations. This study presents a case of a 35-year-old female who underwent endometrial polyp removal 5 days before symptom onset and started using a transdermal estradiol patch. After 4 days of using the transdermal estradiol patch, the patient developed recurrent seizures and sustained sensory aphasia. The head computed tomography revealed hemorrhagic infarction. Given her young age and the use of hormonal therapy, CVST was suspected. However, the initial diagnosis with magnetic resonance imaging (MRI) was inconclusive, and no venous sinus thrombosis could be identified on additional cerebral angiography. Instead, stasis of venous flow in the temporal vein was noted. It was difficult to determine whether these findings were due to hemorrhage or ICVT. Upon re-evaluation with MRI, signal changes suggestive of thrombosis in a cortical vein in the parietal region, which is different from the stasis observed in cerebral angiography, led to the diagnosis of ICVT. This is the first study to link the use of transdermal estradiol patches to ICVT. In cases where ICVT leads to cerebral hemorrhage, cerebral angiography may not be useful. Instead, a comprehensive diagnosis should be made based on imaging findings from various MRI sequences and the patient's medical history.

☆ Acknowledgments: We express our sincere appreciation to the patient who graciously consented to participate in this case report. We would also like to thank enago (https://www.enago.com) for their English language editing services. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
☆☆ Competing Interests: None.
* Corresponding author.
E-mail address: haruhirata0@gmail.com (H. Hirata).
https://doi.org/10.1016/j.radcr.2024.04.062

Introduction

Cerebral venous and sinus thrombosis (CVST) is a rare condition with an annual incidence of up to 15.7 per million per year. Moreover, ICVT—involving a cortical vein without any thrombosis in the major cerebral veins or sinuses—is even rarer, accounting for only 5% of all CVST cases [1]. CVST predominantly affects individuals who are younger on average than those diagnosed with arterial strokes, with women being at a higher risk than men [2]. Conditions, such as protein C deficiency, protein S deficiency, and abnormal fibrinogen levels, can increase prothrombotic states. Acquired hypercoagulable conditions include malignancy, oral contraception use, oncology, pregnancy, estrogen supplementation, hormone replacement therapy, antiphospholipid syndrome, and a history of deep vein thrombosis or pulmonary embolism [1,2], with recent reports also linking it to coronavirus disease (COVID-19) [3]. Diagnostically, computed tomography venography (CTV), magnetic resonance venography (MRV), and cerebral angiography can identify venous defects [4], whereas conventional computed tomography (CT) and magnetic resonance imaging (MRI) can directly visualize the thrombosed vein (cord sign) [5–7]. For treatment, starting anticoagulation therapy early is key, whether or not there is bleeding. If significant swelling can be observed in the brain, decompressive craniectomy may be necessary [8,9].

This study reports a case of ICVT diagnosed through comprehensive findings from CT, MRI, MRV, and cerebral angiography in a patient experiencing seizures, while using a transdermal estradiol patch. To our knowledge, no case reports have focused on the diagnostic methods for ICVT leading to hemorrhagic stroke. Although cases of ICVT are seldomly mentioned in the literature, the present study is the first to report a case of ICVT developing during the application of transdermal estradiol patch.

Case report

This study included a 35-year-old Japanese woman with no significant medical history who was undergoing fertility treatment to conceive her first child. Five days before symptom onset, she underwent a procedure to remove a uterine polyp, and 4 days before symptom onset, she started using a transdermal Estradiol (Estrana Tape, Hisamitsu Pharmaceutical Co., Inc., Tokyo, Japan) (0.72 mg/2 days) to promote endometrial regeneration. She experienced mild headaches and nausea, resulting in reduced food intake, but could otherwise continue her daily activities. Until the night before the event, she exhibited no neurological symptoms. However, on the morning of the symptom onset, she was found in her bed, unable to get up or speak.

Initially, her condition was observed without any intervention. One hour after being discovered in this state, she experienced her first generalized tonic–clonic seizure, which resolved spontaneously within a minute. Following this, she had 2 additional episodes of generalized clonic seizures, each lasting 1 min, before being transported to our hospital. By the time of her arrival, the seizures had stopped. Her vital signs were notable for a fever of 37.8°C, with no other abnormalities. The neurological examination indicated a Glasgow Coma Scale score of E4V2M5 and sensory aphasia. Given the influence of seizures on her condition, treatment with an intravenous infusion of levetiracetam (Keppra, UCB Pharma, Brussels, Belgium) 500 mg was initiated.

The blood workup also revealed an elevated white blood cell count of 17.2 × $10^3/\mu L$, with a neutrophil absolute count of 12.68 × $10^3/\mu L$, lymphocyte absolute count of 3.95 × $10^3/\mu L$, and monocyte absolute count of 0.53 × $10^3/\mu L$. Moreover, the hemoglobin level was 14.5 g/dL, hematocrit level was 44.9%, and uric acid level was 8.8 mg/dL, which were all elevated, indicating possible dehydration. The creatinine level was slightly elevated at 1.07 mg/dL, whereas the blood urea nitrogen level was within the normal range at 8.4 mg/dL. No electrolyte imbalances were observed. The coagulation profile showed a mild elevation in fibrin degradation products at 6.8 μg/mL. Hydration treatment corrected the dehydration and abnormal values by the second day after onset. The results of the screening for thrombophilic factors, including Protein C and S antigen levels and lupus anticoagulant, and the tests for various collagen diseases and anti-neutrophil cytoplasmic antibodies were all within normal ranges. Moreover, COVID-19 was ruled out through antigen and antibody testing.

A head CT scan showed a patchy hyperdense area with surrounding hypodensity in the left temporal lobe, which is suggestive of a hemorrhagic infarction (Fig. 1A). There was no evidence of intravascular thrombosis indicated by hyperdensity. The chest and abdominal CT scans did not reveal any findings suggestive of infection. The MRI findings revealed intracerebral hemorrhage in the left temporal lobe with associated edema (Fig. 1). No abnormal signals indicating thrombosis in the brain cortex surrounding the hemorrhage or venous sinuses were detected. The patient became agitated during the examination, complicating the imaging process. Consequently, imaging with magnetic resonance angiography, MRV, and SWI was not feasible. Considering that the patient was a young woman undergoing hormone therapy, the possibility of CVST was considered, but no diagnosis could be confirmed at this stage. Angiography was performed not only to evaluate CVST but also to investigate the possibility of arterial system involvement and the potential for an arteriovenous shunt. However, no aneurysms, shunt pathologies, or evidence of CVST were recorded. The avascular areas around the hemorrhage and blood flow stasis in the temporal vein were observed; however, it was difficult to determine whether these findings were associated with the effects of the hemorrhage and edema or thrombotic occlusion (Figs. 4B and C).

Based on a detailed review of the MRI sequences, we identified the areas consistent with the course of cortical veins near the vertex, away from the stasis zone. These showed slightly elevated signals on T1-weighted imaging (T1WI) and reduced signals on T2* gradient-echo (T2*) sequences, resulting in a diagnosis of ICVT. Retrospectively, the comparison with the follow-up MRI findings revealed that these areas were also hypointense on T2-weighted imaging (T2WI), although initially, we had interpreted these findings merely as flow voids (Figs. 2A-E).

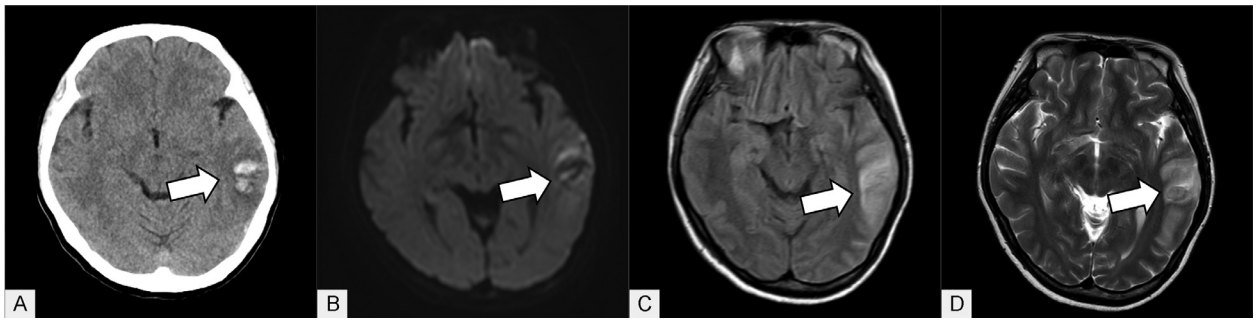

Fig. 1 – Hemorrhagic infarction on the day of onset. Computed tomography revealed patchy high attenuation with surrounding edema in the left temporal lobe (A), which showed high signal with low signal internally (B). On fluid-attenuated inversion recovery imaging, the area around the hemorrhage exhibited high signal intensity (C), whereas on T2* imaging, it ranged from low to high signal intensity.

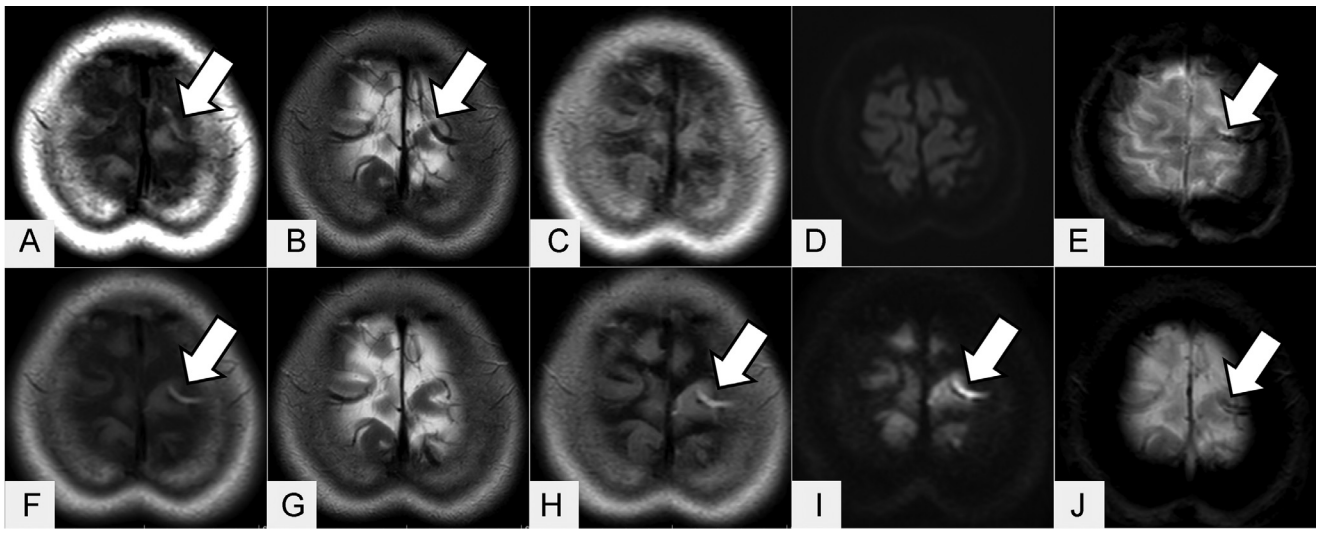

Fig. 2 – Signal changes in cord sign on the day of onset (upper row) and Day 7 (lower row). On the day of onset, intracranial venous thrombosis (arrows) was detected as high signal intensity on T1WI (A) and low signal intensity on T2* gradient-echo image (E). No signal changes were observed on fluid-attenuated inversion recovery (FLAIR) (C) or diffusion weighted imaging (DWI) (D). On Day 7, no signal changes were observed on T1WI (F) and T2* (J) ; however, high signal intensity of the thrombus was noted on FLAIR (H) and DWI (I). The thrombus area on T2WI appeared as a low signal intensity on the day of onset (B) but became indistinct on Day 7 (G).

Treatment with levetiracetam at a dose of 1000 mg/day was started for seizure control, and the transdermal estradiol patch application was halted. To manage coagulation, we started with a continuous intravenous infusion of unfractionated heparin, aiming to achieve an activated partial thromboplastin time that was 2 to 3 times above the baseline value. This was followed by a transition to warfarin (Coumadin, Bristol-Myers Squibb, New York, USA), with the aim of maintaining an international normalized ratio between 2 and 3. Following these interventions, no further bleeding or development of new ischemic areas was observed. Through rehabilitation, the patient gradually regained consciousness, experienced no further seizures, and showed improvement in her previously noted aphasia.

On the seventh day after symptom onset, the follow-up MRI results indicated that the abnormal signal from the thrombus persisted. While no change on T2* was observed, T1WI revealed a higher signal intensity. Moreover, the sequences showed increased signal intensity on fluid-attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI). The thrombus was no longer visible on T2WI (Figs. 2F-J). On Day 17, the high signal on fluid-attenuated inversion recovery imaging had become more pronounced (Fig. 3A), and a high signal was also observed on MRV (Fig. 3B). By creating a 3D model from the MRV images and comparing it with the findings from cerebral angiography at the time of admission (Fig. 4A), an avascular area corresponding to the thrombus site was identified for the first time (Fig. 4B). On Day 28, the level of consciousness and aphasia had completely improved. Angiography showed improvement in the venous return of the temporal vein that was identified on the day of onset (Figs. 4D and E). The avascular area around the venous

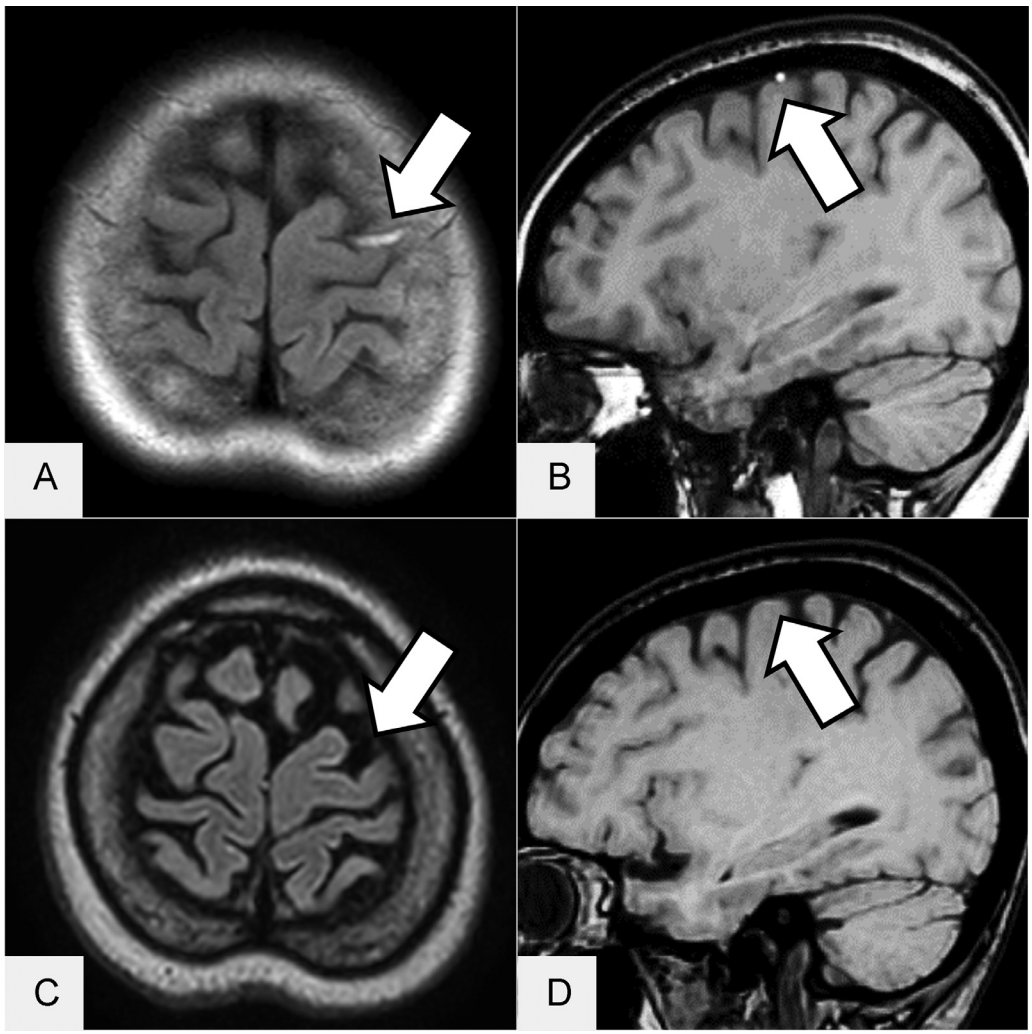

Fig. 3 – Signal changes in cord sign (arrows) on fluid-attenuated inversion recovery (FLAIR) and magnetic resonance venography (MRV) on Days 17 and 112 after onset. On the 17th day, an increased intensity in the signal detected on fluid-attenuated inversion recovery imaging (A), accompanied by the appearance of a heightened signal on MRV (B), was observed. On the 112th day, the heightened signal observed on FLAIR imaging at the location of the thrombus had vanished (C), and the signal on MRV had transitioned to an isointense state, rendering it challenging to differentiate from typical vessels (D).

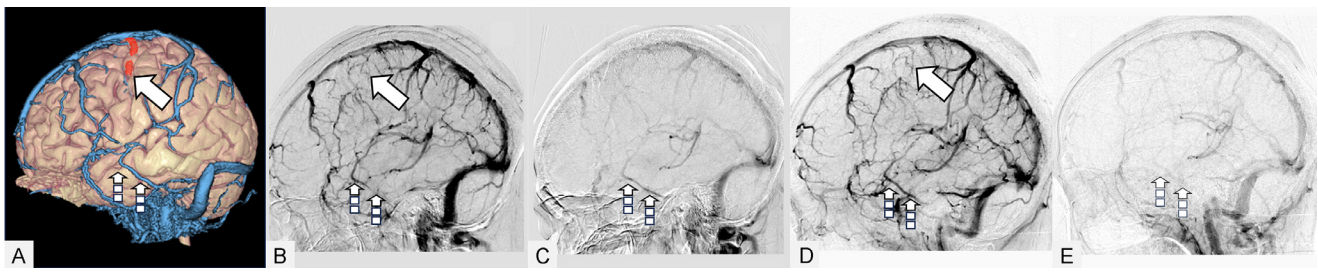

Fig. 4 – 3D model of thrombus and cerebral veins and vascular imaging on the day of onset and 28th day after onset. Comparison of the thrombus formation site on the 3D model constructed from magnetic resonance venography and fluid-attenuated inversion recovery images (A) reveals avascular regions in the cortical vein of the frontal lobe on both the day of onset (B) and Day 28 (D) (arrows). On the day of onset, blood stasis was observed in the cortical vein of the temporal lobe (B,C), which had improved by Day 28 (D,E) (dotted arrow).

thrombus remained unchanged (Fig. 4D). Considering the resumption of fertility treatment, anticoagulation therapy was switched from warfarin, which has potential risks of miscarriage and teratogenicity, to edoxaban (Lixiana, Daiichi Sankyo, Tokyo, Japan). On day 112, the high signal on FLAIR at the thrombus site had disappeared (Fig. 3C), and the signal on MRV had become isointense, making it difficult to distinguish FLAIR from normal vessels (Fig. 3D). Furthermore, edoxaban was discontinued in preparation for the resumption of fertility treatment, and 12 months after symptom onset, the patient has experienced no recurrence of symptoms and is aiming to conceive.

Discussion

In our discussion, we investigated a unique case of ICVT occurring alongside the application of transdermal estradiol patch, considering the challenges of diagnosing ICVT and the critical role of imaging techniques. This case presented diagnostic difficulties, particularly in the presence of hemorrhage, emphasizing the importance of meticulous analysis of various MRI sequences for accurate diagnosis.

For both ICVT and other forms of CVST, anticoagulation therapy at symptom onset is the preferred approach to stop the thrombus from growing and to reopen the blocked vein, regardless of bleeding [8,9]. However, in cases of bleeding, anticoagulation could worsen the bleeding if not properly diagnosed as venous thrombosis. This suggests the need for an accurate diagnosis and careful consideration before initiating anticoagulation therapy in the acute phase, as demonstrated in the present case.

Venous sinus thrombosis can be indirectly diagnosed through MRV, CTV, or cerebral angiography by identifying missing segments of sinuses or veins and compensatory dilation of adjacent veins [4,10,11]. However, diagnosing ICVT can be more challenging than diagnosing venous sinus thrombosis because it is harder to identify areas of blood flow deficit [7]. Plain CT and MRI can be useful because they can directly show the thrombus. On plain CT, the hyper density of a thrombus, known as the cord sign, is considered helpful for diagnosis [6]. MRI can also show an MRI equivalent of the cord sign, but Duncan et al. noted that it can be difficult to identify, especially during the acute stage of thrombosis. This difficulty arises because the clot tends to have the same intensity as the brain on T1WI and is less intense on T2WI, wherein it mimics a flow void [7].

SWI has been identified as highly effective in the direct diagnosis of cerebral cortical vein thrombosis, including cases of ICVT. A recent study by Boukerche et al., which compared MRV with standard MR sequences, focused on 30 instances of cerebral cortical vein thrombosis, of which 2 were ICVT. They found that high-resolution SWI sequences, designed to differentiate cortical vein clots from deoxyhemoglobin in open veins, offered the highest sensitivity and accuracy among standard MR sequences. The study reported a sensitivity of 93%, specificity of 100%, positive predictive value of 100%, negative predictive value of 96%, and overall accuracy of 97%. Although other sequences, such as enhanced 3D magnetization-prepared rapid gradient-echo (MPRAGE), MRV, T1 turbo spin echo (TSE), FLAIR, DWI, T2 turbo spin echo (T2 TSE), and enhanced T1 turbo spin echo with fat saturation, were evaluated for their ability to detect thrombosis, none matched the SWI's performance, with sensitivities ranging from 0.39 to 0.06. Importantly, when SWI was combined with other sequences, the diagnostic efficacy reached 100% sensitivity and accuracy. Based on these findings, MRI that includes SWI is preferable for the direct diagnosis of ICVT [10].

A high level of clinical suspicion and meticulous analysis of sectional imaging, including the observation of temporal changes in the cord sign, are important in the diagnosis of ICVT, especially in the presence of hemorrhage and edema. In our case, the absence of initial assessments with MRV or CTV and the failure of cerebral angiography to reveal venous or sinus defects highlighted the challenges of indirect diagnosis. The complication of cerebral displacement due to hemorrhage further obscured the diagnosis, revealing blood stagnation in areas that were not identified by the cord sign on MRI. This emphasizes the limitations of relying solely on angiography for ICVT diagnosis in patients with hemorrhage or edema. Although patient movement precluded the use of SWI, the identification of the cord sign in other MRI sequences facilitated the diagnosis. By comparing these findings with follow-up MRI sequences and angiographic evidence, we could corroborate the diagnosis by identifying avascular areas that confirmed thrombosis. This case illustrates the importance of actively searching for direct signs of thrombosis, such as the cord sign, and emphasizes the necessity of a high index of clinical suspicion alongside the appropriate and careful use of sectional imaging for an early and accurate diagnosis of ICVT.

In our study, we documented what appears to be the inaugural instance of ICVT arising concurrently with the application of transdermal estradiol patch. In contrast, Vinogradova et al. identified that a comprehensive exposure to hormone replacement therapy over the preceding 90 days correlated with a 43% heightened risk of venous thromboembolism (VTE), specifically noting that oral formulations considerably increased VTE risk, whereas transdermal estradiol patches showed no such association with VTE risk [12]. However, our capability to screen for all variants of hereditary thrombophilia was limited, preventing us from ruling out the influence of other undetected conditions. Nonetheless, given the strong linkage observed between the application of the transdermal estradiol patch and the emergence of ICVT in a patient with a well-documented history of conditions related to the use of transdermal estradiol patches, it can be suggested that the patch has an important role in the formation of thrombosis.

Conclusion

The critical role of imaging in the diagnosis of CVST has been well acknowledged. However, the decision to use specialized imaging techniques, such as SWI, depends heavily on the initial clinical suspicion based on the patient's history. Without this suspicion, crucial imaging may not be performed. This underscores the urgent need for more case reports and investi-

gations to further determine the potential link between the use of transdermal estradiol patches and the development of ICVT.

Declaration of generative AI in scientific writing

During the preparation of this work, the author utilized ChatGPT for partial translation of their own writing as well as for English grammar and spell checking. Following the use of this tool, the author reviewed and edited the content as necessary, taking full responsibility for the publication's content.

Data statement

The data related to this study is restricted by the author's affiliated institution and is available only to researchers who meet specific requirements. For more details, please contact the author.

Patient consent

I hereby certify that I obtained the patient consent for publication on 16th of October 2023.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2024.04.062.

CRediT authorship contribution statement

Haruki Hirata: Conceptualization, Methodology, Writing – original draft. **Yuta Kaneshiro:** Supervision, Writing – review & editing. **Yumiko Urano:** Supervision, Writing – review & editing. **Keiji Murata:** Supervision, Writing – review & editing.

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