

# Delayed diagnosis of spinal subarachnoid hemorrhage in association with warfarin administration: a case report and literature review

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## Abstract

Spinal subarachnoid hemorrhage is a life-threatening condition often associated with markedly high morbidity and mortality rates. However, diagnosis is difficult because of its atypical symptoms. We herein describe a 52-year-old Chinese man who had been receiving warfarin therapy since having undergone mechanical mitral valve replacement surgery 3 years previously. Two days before admission to our hospital, he suddenly developed low back pain, urinary incontinence, and paraplegia. He was diagnosed with acute myelitis at a local hospital, but he subsequently developed a slight headache and was transferred to our hospital 2 days later. The patient was suspected to have subarachnoid hemorrhage based on his computed tomography (CT) findings. On the third day after admission, a CT scan showed both subarachnoid and cerebral hemorrhage. Blood tests revealed an international normalized ratio ranging from 1.44 to 1.86 and a prothrombin time of 16.5 to 21.3 s. We performed a lumbar puncture and obtained bloody cerebrospinal fluid. The patient also underwent spinal CT and angiography, which confirmed the diagnosis of spontaneous spinal subarachnoid hemorrhage. Because his general condition was poor, he underwent conservative treatment, and his neurologic function slightly improved after discharge.

## Keywords

Misdiagnosis, spinal subarachnoid hemorrhage, warfarin, international normalized ratio, prothrombin time, neurologic function

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## Introduction

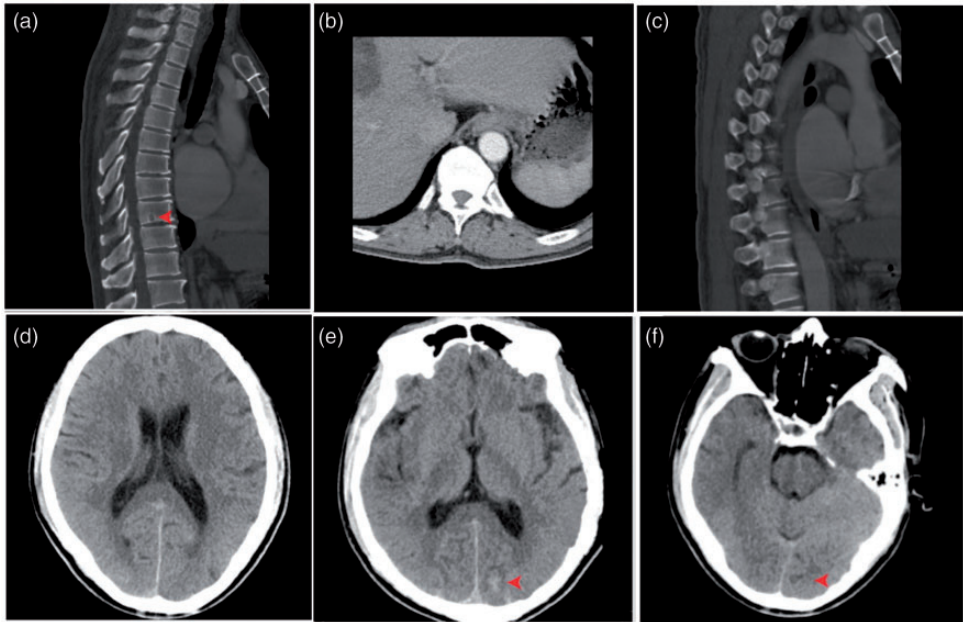
Spinal subarachnoid hemorrhage (SSH) is uncommon, occurring in <1% of all patients with subarachnoid hemorrhage (SAH).<sup>1,2</sup> The causes of SSH include trauma (often by lumbar puncture), vascular lesions (arteriovenous malformation or fistula, aneurysm), coagulopathy, systemic lupus erythematosus, coarctation of the aorta, and Behçet's disease.<sup>3-5</sup> However, hemorrhage in association with anticoagulant therapy is rarely seen. Warfarin is one of the most frequently used anticoagulants to prevent atrial fibrillation as well as venous and arterial thromboembolism.<sup>6</sup> Taking precautions against thromboembolism secondary to mechanical valve replacement is especially important when treating patients with rheumatic heart disease.<sup>7,8</sup> Patients who have undergone implantation of a mechanical valve prosthesis are committed to lifelong anticoagulant therapy with warfarin.<sup>9</sup> However, highly variable dose-related problems exist among patients undergoing warfarin treatment.<sup>7</sup> We herein describe a patient who was initially misdiagnosed with acute myelitis and was subsequently confirmed to have spontaneous SSH based on his clinical symptoms and results of lumbar puncture, spinal angiography, and brain and spinal computed tomography (CT).

## Case report

A 52-year-old Chinese man was admitted to the Department of Neurology at The First Hospital of Changsha on 1 August 2019. He had been continuously taking warfarin at a dosage of 3.125 mg/day since having undergone mechanical mitral valve replacement surgery 3 years previously. His most recent international normalized ratio (INR) had been measured 1 week before presentation, and the result was 2.2. Two days before admission, the patient suddenly

developed low back pain with no obvious cause followed by nausea and vomiting. He was diagnosed with acute myelitis at a local hospital. The next morning, the patient developed a lack of bilateral leg strength, numbness spreading across his feet and chest, urinary incontinence, and a fever of 38.44°C. At the time of admission to our hospital, a CT scan showed no brain abnormalities. A urinary catheter was inserted, and the patient was transferred to the Department of Neurology at our hospital for further examination and diagnosis.

Upon admission, the patient was conscious and alert with a good sense of direction. His back pain had become less severe than that experienced during the occurrence of paraplegia and numbness; however, he developed a mild headache. Physical examination showed flaccid paraparesis in both legs and an obviously rigid neck. His cranial nerves remained intact. Based on the patient's history and neurological test results, we performed a lumbar puncture on the day of admission. The cerebrospinal fluid (CSF) was bloody at all three puncture sites; therefore, we concluded that the attempts had been unsuccessful because of puncture injury. The patient underwent a spinal CT scan, which revealed degenerative change in the lumbar spine and a Schmorl node at T9 (Figure 1(a)–(c)). However, no cauda equina or nerve root compression was observed. An urgent brain CT scan showed no abnormalities. Because the patient had a history of mechanical valve replacement surgery, magnetic resonance imaging was contraindicated. Examination of the peripheral blood showed that the INR was 1.95 and that the prothrombin time (PT) was 1.96 s. On the second day, the patient's brain CT results suggested SAH (Figure 1(d)). We performed another lumbar puncture, and bloody CSF was retrieved again in three test tubes, thus confirming SSH (Figure 3(a)). On the third day, the patient experienced more frequent



**Figure 1.** Computed tomography (CT) findings. (a–c) Spinal CT showed no hemorrhage but revealed degenerative changes in the lumbar region and a Schmorl node of T9. (d) Brain CT results suggested subarachnoid hemorrhage (SAH). (e) A second brain CT examination revealed hyperdense areas in the left posterior occipital region compatible with SAH. (f) Follow-up brain CT conducted 12 days later no longer showed the previously detected hyperdense areas and SAH.

headaches, and the back of his neck grew increasingly more painful. A second brain CT scan showed a high-density area in the left posterior occipital region that was compatible with SAH (Figure 1(e)). Repeated blood tests revealed a PT of 21.3 s and INR of 1.86.

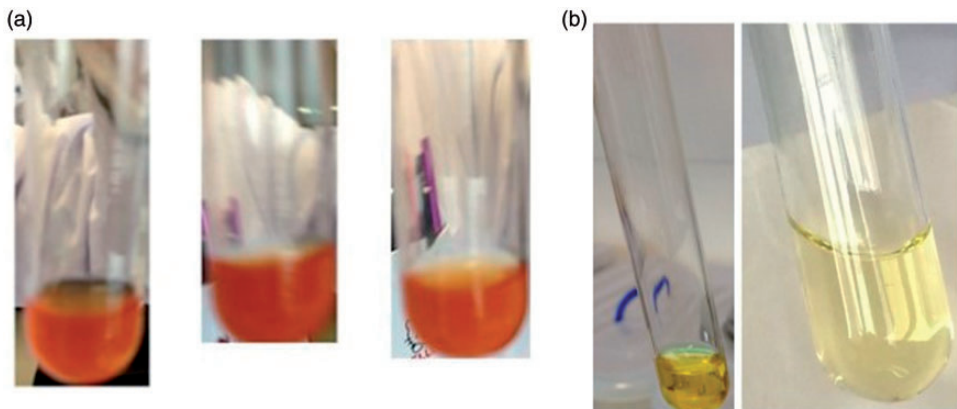
In view of the negative spinal CT results, we performed spinal angiography. Still, no arteriovenous malformation or other vascular abnormalities were found (Figure 2(a)–(e)). Considering the patient's medical history and clinical manifestations, we temporarily stopped his anticoagulation treatment and administered vitamin K to reverse the anticoagulation, aminocaproic acid to induce hemostasis, and nimodipine to prevent vasospasm; we also performed CSF replacement. Continuous lumbar punctures produced fluid containing hemorrhage and

yellow pigmentation (Figure 3(b)). The high-density area in the left posterior occipital region and the SAH markers were negative after 12 days of follow-up (Figure 1(f)). Therefore, the patient restarted his warfarin treatment at 1.25 mg/day. At this time point, his PT and INR were 16.5 s and 1.44, respectively. Three days later, we adjusted his warfarin dosage to 2.5 mg/day. Another 2 days later, the patient developed nasal hemorrhage with a PT of 17.3 s and INR of 1.52. Nasal endoscopy examination revealed chronic rhinitis with no other abnormalities. Therefore, we adjusted the warfarin dosage to 1.875 mg/day. Neither nasal bleeding nor cerebral or spinal hemorrhage occurred thereafter.

The SSH in this case was presumed to have developed as a result of the oral anti-coagulant therapy based on the rise in the



**Figure 2.** Spinal angiography demonstrated no evidence of an arteriovenous malformation or other vascular abnormality.



**Figure 3.** Lumbar puncture results. (a) Lumbar puncture yielded bloody cerebrospinal fluid and positivity on a three-tube test. (b) Two sequential lumbar puncture tests revealed hemorrhage and xanthochromia.

PT and INR. Therefore, the dosage was altered accordingly. Because the patient's general condition was relatively weak and continuous anticoagulation treatment is more effective than sporadic treatment, we performed no surgical treatments. The patient was finally discharged 32 days after admission. Some functional improvements were observed after discharge; he became able to move himself with a standing turner and the assistance of another person instead of entirely depending on others.

## Discussion

SSH rarely occurs, accounting for <1% of all cases of SAH.<sup>10,11</sup> It may be caused by trauma, arteriovenous malformation, arteriovenous fistulas, aneurysms, tumors, vasculitis (systemic lupus erythematosus, Behçet's disease), bleeding diatheses, or anticoagulant therapy.<sup>10</sup> However, the etiology of SSH is not entirely clear. It is generally believed that minor trauma can increase the intrathoracic, intraluminal, and intra-abdominal pressure among spinal vessels, especially the valveless radiculomedullary veins traversing the subarachnoid space, resulting in torn vessels.<sup>2,10</sup> Lumbar puncture with CSF replacement can relieve symptoms of SAH. Defibrination caused by spinal cord pulsation can reduce the possibility of a subarachnoid hematoma. If bleeding becomes chronic; however, the CSF mechanism will fail to neutralize this force, resulting in potential clotting. Therefore, close attention to the use of anticoagulant drugs is required.

Anticoagulant therapy is often complicated by hemorrhage.<sup>8</sup> Our patient developed spontaneous SSH accompanied by cranial and nasal hemorrhage while receiving warfarin therapy, although his INR and PT were normal. Therefore, he required monitoring with coagulation studies to

minimize the chance of complications during anticoagulant therapy as well as adjustments to his warfarin dosage.<sup>12</sup> Insufficient or excessive use of anticoagulants can be life-threatening, and the risk of thromboembolism and bleeding depends largely on anticoagulation therapy. Both the British Society for Haematology and the American College of Chest Physicians suggest that the INR range for most warfarin indications is 2 to 3.<sup>13</sup> In practice, however, it is challenging to keep the INR within that range.<sup>14,15</sup> Ming and Klein<sup>16</sup> reported that only 44% of patients achieved a satisfactory INR. The anticoagulation effect of warfarin is subject to individual variability, leading to possible hemorrhage or thrombosis despite careful dosage adjustments.<sup>8</sup> Yuan<sup>7</sup> reported that Chinese patients generally need a lower warfarin dose than Caucasians. You et al.<sup>14</sup> conducted a retrospective study in Hong Kong showing that the best INR range was 1.8 to 2.4 in a group of Chinese patients; this range was associated with the lowest incidence of bleeding or thromboembolism.

Typical symptoms of SSH include sudden back pain, severe headache, quadriplegia, paraplegia, numbness, sensory change, and urinary or fecal incontinence. The clinical manifestations are markedly diverse among different individuals. Physical examination generally shows different degrees of defects in motor, sensory, and sphincter functions that are correlated with the degree of pathological changes. Therefore, it is difficult for doctors to make a correct judgment in the beginning of the patient's clinical course, leading to misdiagnosis as reported in the present case. Our patient developed no severe headache attacks and showed normal brain CT findings, and he was misdiagnosed with acute myelitis at a local hospital. Even with advanced neuroimaging techniques, the diagnosis of SSH is often challenging.<sup>3</sup>

Magnetic resonance imaging is an essential method with which to identify SSH because it can show the size and extension of the hemorrhage and its relationship with the spinal cord.<sup>8</sup> However, the role of CT in the diagnosis of SSH is limited. As described in the present case, only spinal and head CT can be performed for patients who have undergone mechanical valve replacement surgery. No positive results were found in either examination, leading to difficulty observing the hemorrhagic lesion. If the presence of a vascular pathology is considered during the diagnostic procedures, selective spinal angiography should be performed to exclude an arteriovenous malformation or aneurysm. Similarly, acquisition of bloody CSF by lumbar puncture may help the clinician to diagnose SSH. However, SSH may exhibit more bleeding than SAH; the CSF may be bloodlike and considered to be a puncture injury, which will affect the diagnosis. In the present case, the first CSF examination revealed “bloody” fluid, but we considered this to be a consequence of puncture injury. Cihangiroglu et al.<sup>12</sup> reported that the majority of SSH cases were diagnosed based on surgical or autopsy findings. Therefore, SSH should not be missed in patients with acute paraplegia, especially those with severe back pain and headache. When lumbar puncture shows “bloody” CSF, it should not be mistaken for puncture injury when performing subsequent punctures.

Most researchers advocate treating SSH by emergency surgery.<sup>17</sup> Such treatment can reduce compression, restore the free flow of CSF, and reduce mortality. Patient recovery after the operation depends on the nerve condition and onset time. In a literature review by Kreppel et al.,<sup>18</sup> patients who received treatment within 12 hours after disease onset showed the highest recovery rate (65.9%), while patients who received treatment within 13 hours to 1 week after

disease onset showed a recovery rate of only 29%. Surgical treatment is not suitable for patients with a relatively weak general condition. The postoperative recovery effect is reportedly poor in patients with complete paraplegia.<sup>19,20</sup> In the present case, the patient was diagnosed with spontaneous SSH, and because he had been taking warfarin, surgery may have been associated with significant risks. Therefore, we chose conservative treatment for him.

## Conclusion

In the present case, a patient with acute paraplegia accompanied by severe back pain and headache and whose lumbar puncture showed “bloody” CSF was easily considered to have sustained a puncture injury; he was misdiagnosed with acute myelitis, delaying the treatment of SSH. Patients who have undergone mechanical valve replacement require long-term oral anticoagulation therapy with warfarin. Even if their INR is lower than the standard of 2 to 3, they are at risk of bleeding and SSH.

## Ethics statement

We have concealed the patient’s details in this pathological report to ensure that his identity is not revealed in any way. Thus, neither ethics committee nor institutional review committee approval was required. The patient described in this report provided oral informed consent.


## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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**References**

1. Kappler SB and Davis JE. An uncommon cause of acute back pain: spinal subarachnoid hemorrhage progressing to spinal cord compression. *J Emerg Med.* 2014; 48: 432–435.
2. Oji Y, Noda K, Tokugawa J, et al. Spontaneous spinal subarachnoid hemorrhage after severe coughing: a case report. *J Med Case Rep.* 2013; 7: 274.
3. Sato K, Roccatagliata L, Depuydt S, et al. Multiple aneurysms of thoracic spinal cord arteries presenting with spinal infarction and subarachnoid hemorrhage: case report and literature review. *Neurosurgery.* 2012; 71: E1053.
4. Govindarajan R and Salgado E. Spinal subarachnoid hemorrhage mimicking a carotid artery dissection. *Neurosurgery.* 2011; 69: E787–E788.
5. Chung J, Park IS, Hwang S-H, et al. Acute spontaneous spinal subdural hematoma with vague symptoms. *J Korean Neurosurg Soc.* 2014; 56: 269.
6. Bruce-Brand RA, Colleran GC, Broderick JM, et al. Acute nontraumatic spinal intradural hematoma in a patient on warfarin. *J Emerg Med.* 2013; 45: 695–697.
7. Yuan, H.-Y. A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. *Hum Mol Genet.* 2005; 14: 1745–1751.
8. Krynetskiy E and McDonnell P. Building individualized medicine: prevention of adverse reactions to warfarin therapy. *J Pharmacol Exp Ther.* 2007; 322: 427–434.
9. Wang MS, Lang X, Cui S, et al. Clinical application of pharmacogenetic-based warfarin-dosing algorithm in patients of Han nationality after rheumatic valve replacement: a randomized and controlled trial. *Int J Med Sci.* 2012; 9: 472–479.
10. Kakitsubata Y, Theodorou SJ, Theodorou DJ, et al. Spontaneous spinal subarachnoid hemorrhage associated with subdural hematoma at different spinal levels. *Emerg Radiol.* 2010; 17: 69–72.
11. Fatehi F, Basiri K and Ghorbani A. Spinal subarachnoid hemorrhage accompanied with intraventricular hemorrhage. *J Res Med Sci.* 2013; 18(Suppl 1): S86–S88.
12. Cihangiroglu M, Bulut S and Nayak S. Spinal subarachnoid hemorrhage complicating oral anticoagulant therapy. *Eur J Radiol.* 2001; 39: 176–179.
13. Lam MPS and Cheung BMY. The pharmacogenetics of the response to warfarin in Chinese. *Br J Clin Pharmacol.* 2011; 73: 340–347.
14. You JHS, Chan FWH, Wong RSM, et al. Is INR between 2.0 and 3.0 the optimal level for Chinese patients on warfarin therapy for moderate-intensity anticoagulation? *Br J Clin Pharmacol.* 2005; 59: 582–587.
15. Zhao L, Chen C, Li B, et al. Verification of pharmacogenetics-based warfarin dosing algorithms in Han-Chinese patients undertaking mechanical heart valve replacement. *Plos One.* 2014; 9: e94573.
16. Ming TML and Klein TE. Pharmacogenetics of warfarin: challenges and opportunities. *J Hum Genet.* 2013; 58: 334–338.
17. Moyer TP, Kane DJ, Baudhuin LM, et al. Warfarin sensitivity genotyping: a review of the literature and summary of patient experience. *Mayo Clin Proc.* 2009; 84: 1079–1094.
18. Kreppel D, Antoniadis G and Seeling W. Spinal hematoma: a literature survey with meta-analysis of 613 patients. *Neurosurgery Rev.* 2003; 26: 1–49.
19. Brilstra EH, Rinkel GJ, Algra A, et al. Rebleeding, secondary ischemia, and timing of operation in patients with subarachnoid hemorrhage. *Neurology.* 2000; 55: 1656.
20. Oz O, Akgun H, Yücel M, et al. Cerebral venous thrombosis presenting with subarachnoid hemorrhage after spinal anesthesia. *Acta Neurologica Belgica.* 2011; 111: 237–240.