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Spontaneous Spinal Subdural Hematoma Secondary to Hemophilia A and Zanubrutinib

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Abstract

Spontaneous spinal subdural hematomas (SSH) are rare occurrences that can occur most commonly secondary to vascular malformations or coagulopathies. Only a small fraction of spontaneous SSHs are caused by acquired coagulation disorders such as leukemia, hemophilia, and thrombocytopenia. This case report describes a patient with a history of Guillain–Barré syndrome (GBS), hemophilia A, and mantle cell lymphoma, on zanubrutinib therapy, a Bruton tyrosine kinase inhibitor associated with a risk of spontaneous hemorrhage. This patient developed a spontaneous spinal subdural hematoma, most likely due to the zanubrutinib therapy and exacerbated due to hemophilia. Treatment was delayed due to the patient's history of GBS that confounded the clinical diagnosis. This case is the first report of a spontaneous SSH in a patient on zanubrutinib, highlighting the need for a high index of suspicion for CNS hemorrhage in patients on Bruton's tyrosine kinase (BTK) inhibitor therapy.

Keywords
- hemophilia
- zanubrutinib
- spinal subdural hematoma
- hemorrhage
- mantle cell lymphoma

Introduction

Spinal subdural hematomas (SSH) are a rare entity. Etiologies for SSH most often involve posttraumatic or iatrogenic causes although a subset of SSH are spontaneous secondary to vascular malformations or coagulopathies.[1] Previous reviews have demonstrated that 10 to 35% of spontaneous SSH are secondary to anti-coagulation therapy, while 4 to 19% are secondary to acquired coagulation disorders such as leukemia, hemophilia, thrombocytopenia, polycythemia vera, and cryoglobulinemia.[1–3]

This case is the first reported spontaneous spinal subdural hematoma in a patient with a history of hemophilia A and mantle cell lymphoma on zanubrutinib treatment. The case was also unique in that in addition to the patient's acquired coagulation issues, the patient had a history of Guillain–Barré syndrome that resulted in an initial misdiagnosis before appropriate imaging was

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obtained and the patient was transferred for surgical intervention.

Case Report

A 76-year-old man with a history of hemophilia A and mantle cell lymphoma presented to an outside hospital for abdominal pain. He was initially diagnosed with mantle cell lymphoma (MCL) (TP53 mutated) 2 years ago by tissue biopsy, with CD5-positive monoclonal B cells identified by flow cytometry and t11;14 by fluorescence in situ hybridization (FISH). His hemophilia was mild with baseline factor VIII activity of 16% without inhibitor. His mantel cell lymphoma was diagnosed 2 years prior, with CD5-positive monoclonal B cells with 11:14 translocation identified by FISH. He underwent six cycles of rituximab–bendamustine, but was complicated by prolonged neutropenia requiring growth factor administration. Two months after completing bendamustine, he was admitted for neutropenic fever and diarrhea and diagnosed with *Campylobacter colitis* and bacteremia. Following this, he experienced ascending weakness involving all extremities, and was diagnosed with Guillain-Barré syndrome confirmed by EMG, requiring plasmapheresis and IVIG with one episode of relapse and ultimate complete neurological recovery. Twenty-two months following his initial diagnosis, he developed recurrence of his MCL and was started on zanubrutinib, at half dose due to his hemophilia A.

He had been on zanubrutinib for 4 months when he presented to the outside hospital, at which time he was diagnosed with gallstones with bile duct dilation and underwent endoscopic retrograde cholangiopancreatography. Forty-eight hours after presentation, the patient experienced ascending numbness and weakness involving the bilateral lower extremities and lower abdomen and midline back pain. Given his history of Guillain–Barré syndrome, he was treated with IVIG and steroids for presumed relapse. A spinal magnetic resonance imaging (MRI) was performed due to lack of improvement that demonstrated an intradural extramedullary lesion at the level of T10–11 with compression on the adjacent spinal cord (►**Fig. 1**). This imaging also demonstrated subacute hemorrhagic fluid within the thecal sac extending caudally from T10 encasing the spinal cord and cauda equina. He was transferred to Moffitt Cancer Center for definitive neurosurgical evaluation.

At the time of transfer, the patent was an American Spinal Injury Association (ASIA) Grade B. He had no motor function in the lower extremities, a T10 sensory level, and upgoing Babinski reflexes. Laboratory studies on admission were significant for thrombocytopenia (103 k/μL) but normal factor VIII activity (74%), PTT, and PT/INR. He was not hypertensive during his inpatient course.

The patient underwent T10–11 laminectomy and evacuation of subacute intradural hematoma causing the most significant compression of the spinal cord at T10 (►**Fig. 2**). No underlying vascular lesion or clear mass was identified. Postoperatively, the patient obtained relief of midline pain and improvement in sensation of the lower extremities, without significant changes in strength. In the perioperative period, the patient was administered von Willebrand factor every 12 hours to maintain normal Factor VIII activity and prevent hemorrhagic complications.

Discussion

Spontaneous spinal hematomas without underlying vascular or mass lesion are an uncommon pathologic entity. A systematic review of the literature reporting on 151 patients (ranging from 6 months to 87 years) with nontraumatic spontaneous acute spinal subdural hematomas found a small increased incidence between the first and second decades of life, with a major peak at the age of 60 years.[3] In a different retrospective review of published reports of spontaneous SSH from 1948 to 2014, 122 cases were identified and 44% of cases was associated with the use of an anti-coagulant.[2] Only 4% was associated with an acquired coagulation disorder, of which only one case was related to hemophilia.[2] Separate reports of hemophilia A and B has shown an association with spontaneous spinal hematomas, being reported in both pediatric and adult patients.[4–7] These have been reported in less than 0.2 to 0.8% of children with hemophilia also with abnormal coagulation cascade factor activity.[8,9]

The patient in this case had a complicated medical history that allowed several potential risk factors that could have contributed to his risk of spontaneous SSH. In addition, his history of Guillain–Barré syndrome, confounded the diagnosis that delayed definitive treatment. Although the patient's history of hemophilia puts him at a slight risk for spontaneous SSH, as demonstrated in previous reviews, it is likely that zanubrutinib played a strong role in his risk of spontaneous hemorrhage.

Zanubrutinib, a second-generation Bruton's tyrosine kinase (BTK) inhibitor, is used as a treatment of relapsing mantle cell lymphoma (MCL). BTK is expressed on B lymphocytes, myeloid cells, and platelets. However, BTK inhibitors can have "off-target" kinase inhibitions (e.g., EGFR, TEC, and Src family kinases) that can lead to certain toxicities (e.g., atrial fibrillation, skin rash, and diarrhea). The pathophysiology of increased bleeding risk associated with BTK inhibitors is currently not well understood and is thought to be mediated by inhibiting platelet activation, aggregation, and thrombus formation possibly through the inhibition of Src family kinases.[10,11] Second-generation BTK inhibitors, including zanubrutinib, were developed to more selectively target BTK while exhibiting less off-target activity, decreasing the adverse side-effect profile.[12] A study of zanubrutinib for MCL reported 9.4% bleeding adverse events though none within the central nervous system, while a recent review found a range of reported bleeding events in 3 to 36% of patients on BTK inhibitor therapy for B cell malignancies.[13,14] Though hemorrhage is a consistently reported adverse reaction of zanubrutinib, CNS involvement appears extraordinarily rare without any reported cases of spontaneous spinal hematomas.[12]

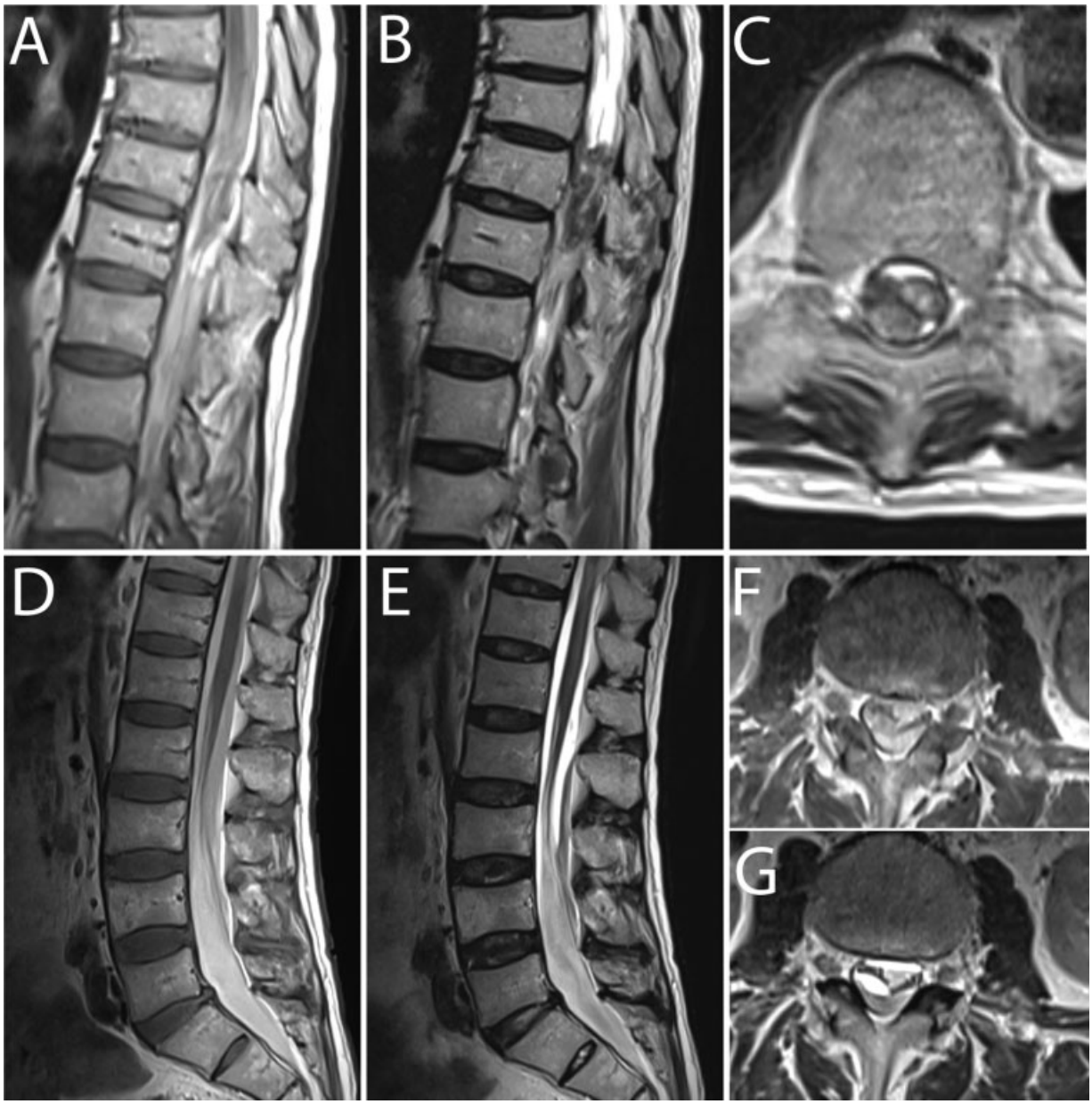

Fig. 1 (**A**) Preoperative sagittal T1-weighted image of the thoracic spine, demonstrating extensive isointense and hyperintense signal reflecting intrathecal blood products. (**B**) Preoperative sagittal and (**C**) axial T2-weighted image of the thorax, demonstrating dorsolateral acute subdural hematoma with greatest degree of spinal cord compression at the level of T10. (**D, E**) Preoperative sagittal T1-weighted and T2-weighted images showing extensive, relatively homogenously hyperintense acute blood through the distal lumbosacral intradural space. (**F, G**) Preoperative axial T1-weighted and T2-weighted sequences of the level of L5, demonstrating casting of the thecal sac by blood products with clumping of spinal nerve roots encased in hematoma.

Although the etiology for the spontaneous SSH in this case is likely a combination of hemophilia and zanubrutinib, it is unclear as to whether there may have been an inciting event that led to the hemorrhage 48 hours following admission to the outside hospital and an ERCP procedure. Possibilities may include an occult trauma to the spine or a hypertensive episode secondary to pain following the procedure. In this case, diagnosis was delayed due to the confounding history of Guillain–Barré syndrome although the presentation was not consistent in that both motor and sensory functions were impaired. This scenario highlights the need for awareness of acute central nervous system-related hemorrhages in a patient with an underlying acquired coagulation disorder while on a medication with a risk for hemorrhage. Acute onset of these symptoms should raise suspicion for an acute neurological event that warrants immediate work-up that should include MRI of the spine.

In addition to spontaneous SSH, the risk of iatrogenic SSH is elevated as a nearly half of previously spontaneous SSH are secondary to iatrogenic causes, such as lumbar puncture, with an underlying coagulopathy.[3] Therefore, the risk of a

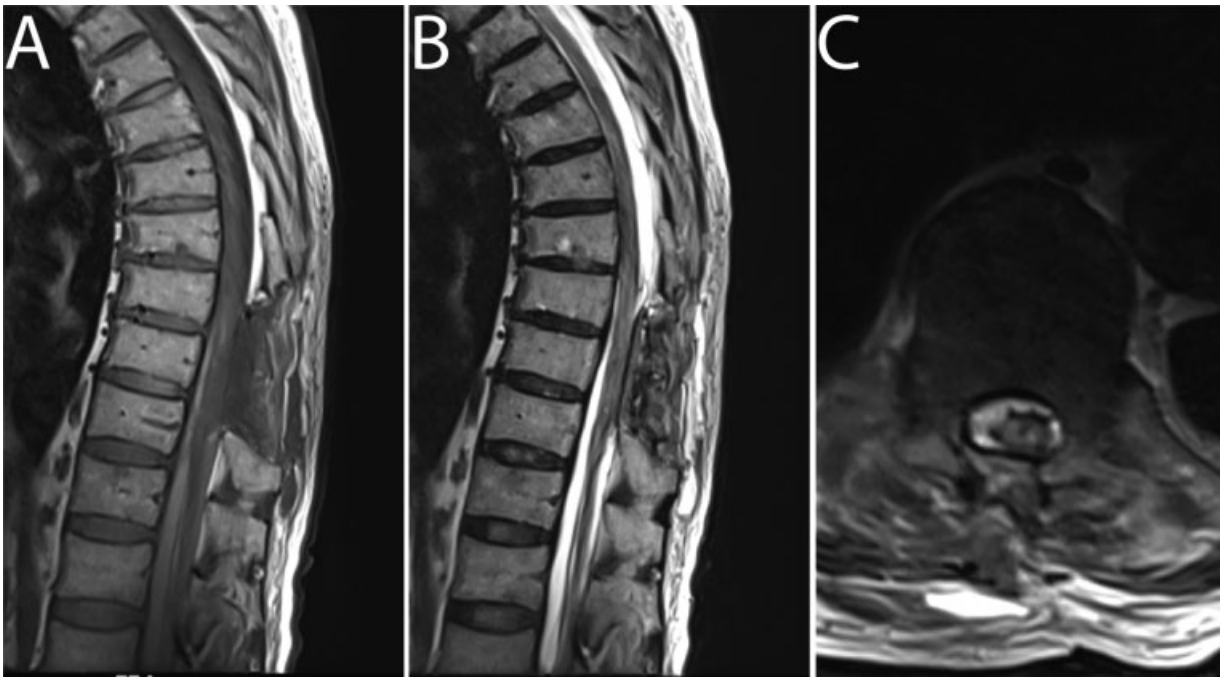

Fig. 2 (**A**) Postoperative sagittal T1-weighted MRI sequence image of the thorax, demonstrating evacuation of focal hematoma. (**B, C**) Postoperative sagittal and axial T2-weighted MRI sequence image of the thorax, demonstrating circumferential hyperintense signal of CSF surrounding the spinal cord, reflecting effective decompression.

SSH needs to be accounted for when considering invasive procedures on these patients.

Conclusion

Spontaneous spinal subdural hematomas can occur in the presence of acquired coagulation disorders, such as hemophilia and BTK inhibitor therapy. This case highlights the need for maintaining a high index of suspicion of spontaneous hemorrhage in the central nervous system while on this type of therapy.

Conflict of Interest
None declared.

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