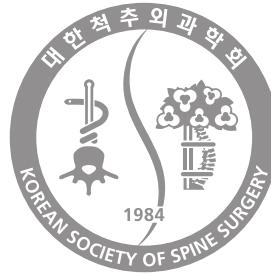


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Cervical Epidural Hematoma and Cord Compression in a Hemophilia A Patient with Elevated Factor VIII Inhibitor Levels after Minor Trauma: A Case Report

Soo Hyun Oh, M.D., Jae-Won Shin, M.D., Ph.D.* Ahn Won Kee, M.D., Ph.D.†, Hak-Seong Seo, M.D., Hak-Sun Kim, M.D., Ph.D.*
Seong-Hwan Moon, M.D., Ph.D.* Kyung-Soo Seok, M.D., Ph.D.* Si-Young Park, M.D., Ph.D.* Byung-Ho Lee, M.D., Ph.D.*
Ji-Won Kwon, M.D., Ph.D.* Hae Won Lee, M.D., Ph.D.†, Jung Woo Han, M.D., Ph.D.†, Seungmin Hahn, M.D., Ph.D.†

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Department of Orthopedic Surgery, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Korea
Tel: +82-31-713-3413

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Cervical Epidural Hematoma and Cord Compression in a Hemophilia A Patient with Elevated Factor VIII Inhibitor Levels after Minor Trauma: A Case Report

Soo Hyun Oh, M.D., Jae-Won Shin, M.D., Ph.D.*[†], Ahn Won Kee, M.D., Ph.D.[†], Hak-Seong Seo, M.D., Hak-Sun Kim, M.D., Ph.D.*[†], Seong-Hwan Moon, M.D., Ph.D.*[†], Kyung-Soo Seok, M.D., Ph.D.*[†], Si-Young Park, M.D., Ph.D.*[†], Byung-Ho Lee, M.D., Ph.D.*[†], Ji-Won Kwon, M.D., Ph.D.*[†], Hae Won Lee, M.D., Ph.D.*[†], Jung Woo Han, M.D., Ph.D.*[†], Seungmin Hahn, M.D., Ph.D.*[†]

Department of Orthopaedic Surgery, Gwangmyeong Sungae Hospital, Gwangmyeong, Korea

**Department of Orthopedic Surgery, College of Medicine, Yonsei University, Seoul, Korea*

†Department of Pediatric Hematology-Oncology, Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea

Study Design: Case report

Objectives: To present a rare case of cervical epidural hematoma caused by mild cervical trauma in a Hemophilia A patient with factor VIII inhibitor.

Summary of Literature Review: Spinal epidural hematoma is a rare but serious condition that can cause acute neurological deficits. Coagulopathies, including hemophilia, are uncommon but important etiologies.

Materials and Methods: A 54-year-old male patient with hemophilia A and an elevated factor VIII inhibitor level presented with right upper and lower extremity motor weakness due to a cervical epidural hematoma superimposed on ossification of the posterior longitudinal ligament. Adequate decompression was achieved through cervical laminoplasty. After admission to the hematology department, meticulous perioperative management was implemented to minimize bleeding risk, enabling surgery to be performed safely.

Results: The patient showed marked neurological recovery following surgery and was discharged without any notable postoperative complications.

Conclusions: This case shows that not just rapid, but also safe surgery by a multidisciplinary approach is important in treating epidural hematomas in hemophilia patients.

Key words: Hemophilia A, Ossification of Posterior Longitudinal Ligament, Epidural hematoma, Laminoplasty, Recombinant factor VII replacement

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Corresponding author: Jae-Won Shin, M.D., Ph.D.

Department of Orthopaedics, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, Republic of Korea

TEL: +82-2-2228-2192, **FAX:** +82-2-363-1139

E-mail: jaewuni@yuhs.ac

Corresponding author: Ahn Won Kee, M.D., Ph.D.

Department of Pediatrics, Yonsei University College of Medicine, 50-1 Yonsei-Ro, Seodaemun-Gu, Seoul, Republic of Korea

TEL: +82-2-2228-2050, **FAX:** +82-2-393-9118

E-mail: TOYRJ87@yuhs.ac

ORCID ID: Soo Hyun Oh: <https://orcid.org/0009-0001-7739-8219>

Jae-Won Shin: <https://orcid.org/0000-0002-6656-6336>

Ahn Won Kee: <https://orcid.org/0000-0003-3668-7396>

Hak-Sun Kim: <https://orcid.org/0000-0002-8330-4688>

Seong-Hwan Moon: <https://orcid.org/0000-0002-5165-1159>

Kyung-Soo Suk: <https://orcid.org/0000-0003-0633-2658>

Si-Young Park: <https://orcid.org/0000-0002-1216-901X>

Byung-Ho Lee: <https://orcid.org/0000-0001-7235-4981>

Ji-Won Kwon: <https://orcid.org/0000-0003-4880-5310>

Hae Won Lee: <https://orcid.org/0000-0002-6088-7470>

Jung Woo Han: <https://orcid.org/0000-0001-8936-1205>

Seungmin Hahn: <https://orcid.org/0000-0001-9832-6380>

Introduction

Spinal epidural hematoma is a rare but important disorder that can lead to permanent neurological deficits and even death. Diverse etiologies were reported including idiopathic, iatrogenic(such as spinal anesthesia on patients with anticoagulant therapy), and vascular malformations. Another rare but important etiology for spinal epidural hematoma is a coagulopathic disorder such as hemophilia.¹⁾ Hemophilia A, a congenital disorder caused by factor VIII deficiency, increases the risk of musculoskeletal bleeding. The risk of bleeding is influenced by factor levels and the presence of inhibitors. While central nervous system hemorrhage occurs in 2–8% of patients with hemophilia A, spinal epidural hematomas are extremely rare.¹⁾

Case Presentation

This case report was carried out following approval from the institutional review board of the hospital (IRB number: 4-2024-1482).

54-year-old male patient who had been diagnosed with hemophilia A with high titer factor VIII inhibitors experienced a sudden tingling sensation and mild weakness in his right upper/lower extremities. This occurred 30 minutes after he received a neck and shoulder massage due to his chronic neck discomfort. After 4 hours, he started to lose his balance and slipped while he was on his way to the bathroom and struggled for urination. After 12 hours, noticing right side motor weakness got worse, he initially visited the emergency department (ED) of a local hospital, where he usually managed his spontaneous hemarthrosis and pain on both hip and right knee.

Cervical spine magnetic resonance imaging (MRI) was performed and revealed cervical cord compression due to an epidural hematoma, predominantly on the right posterior side of the cervical cord from C2 to C4. Along with pre-existing OPLL from C2 to C6, epidural hematoma was compressing the cord anteriorly (Fig 1.) To prevent further hematoma formation and activate the extrinsic coagulation pathway instead, recombinant factor VIIa (Novoseven® (Novo Nordisk A/S, Bagsvaerd, Denmark)), which was usually injected for his recurrent hemarthrosis events, was immediately injected. He was recommended for surgery, but perioperative care for PwHA was not possible in his local rural area. He called Korea

Hemophilia Foundation for help, and the patient was finally transferred to our institution, 36 hours after the injury.

On neurological examination after transfer to our hospital, the patient exhibited grade 1–2 motor strength in the right upper extremity and grade 3 motor strength in the right lower extremity (Table 1). The right-side hip flexor (L2) and knee extensor (L3) motors were not evaluable because of joint contractures, which are attributable to previous repetitive hemarthrosis. On the contrary, the left side upper and lower extremity motors were all preserved as grade 5, and the patient's sensation was relatively preserved, only showing 'glove-like hypoesthesia' on both of his hands. Hoffmann signs and ankle clonus signs were not definite. The patient was admitted to the Hematology department for pre- and post-operative care.

In the blood tests performed in the ED, the patient's platelet count was $223 \times 10^3/\mu\text{L}$ which was within the normal range (normal: $150 \times 10^3 \sim 400 \times 10^3/\mu\text{L}$). Prothrombin time (PT) was undetectable because coagulation time was so rapid in the lab test, maybe due to the effect of Novoseven® administered in the local hospital just before transfer. (normal: 9.2~13.1 seconds) Activated partial thromboplastin time (aPTT) was slightly prolonged at 44.4 seconds (normal: 26.8~40.6 seconds), which was not prolonged much, like most of the other PwHA with inhibitors.

Consequently, we conducted additional factor VIII and inhibitor assays to further evaluate the patient's coagulation profile. After a 5-day turn-around time, the factor assay revealed no detectable factor VIII inhibitors and a factor VIII level of 5%. However, given the urgency of the situation and the need for emergency surgery, we could not wait for the assay results and decided to use Novoseven® agent for perioperative bleeding control.

After administering Novoseven® every 3 hours for a day, the patient underwent the operation (72 hours after the injury). Laminoplasty from C3 to C6, with partial dome laminectomy of C2 and C7, was performed. Because the epidural hematoma was predominantly on the right posterior side of the cord, laminas were opened and firmly fixated with laminoplasty plates on the patient's right side (Fig 2.) Hematoma was evacuated, and adequate decompression was achieved. Estimated blood loss (EBL) was minimal.

Until 5 days postoperatively, Novoseven® and tranexamic acid were administered to reduce the risk of hematoma

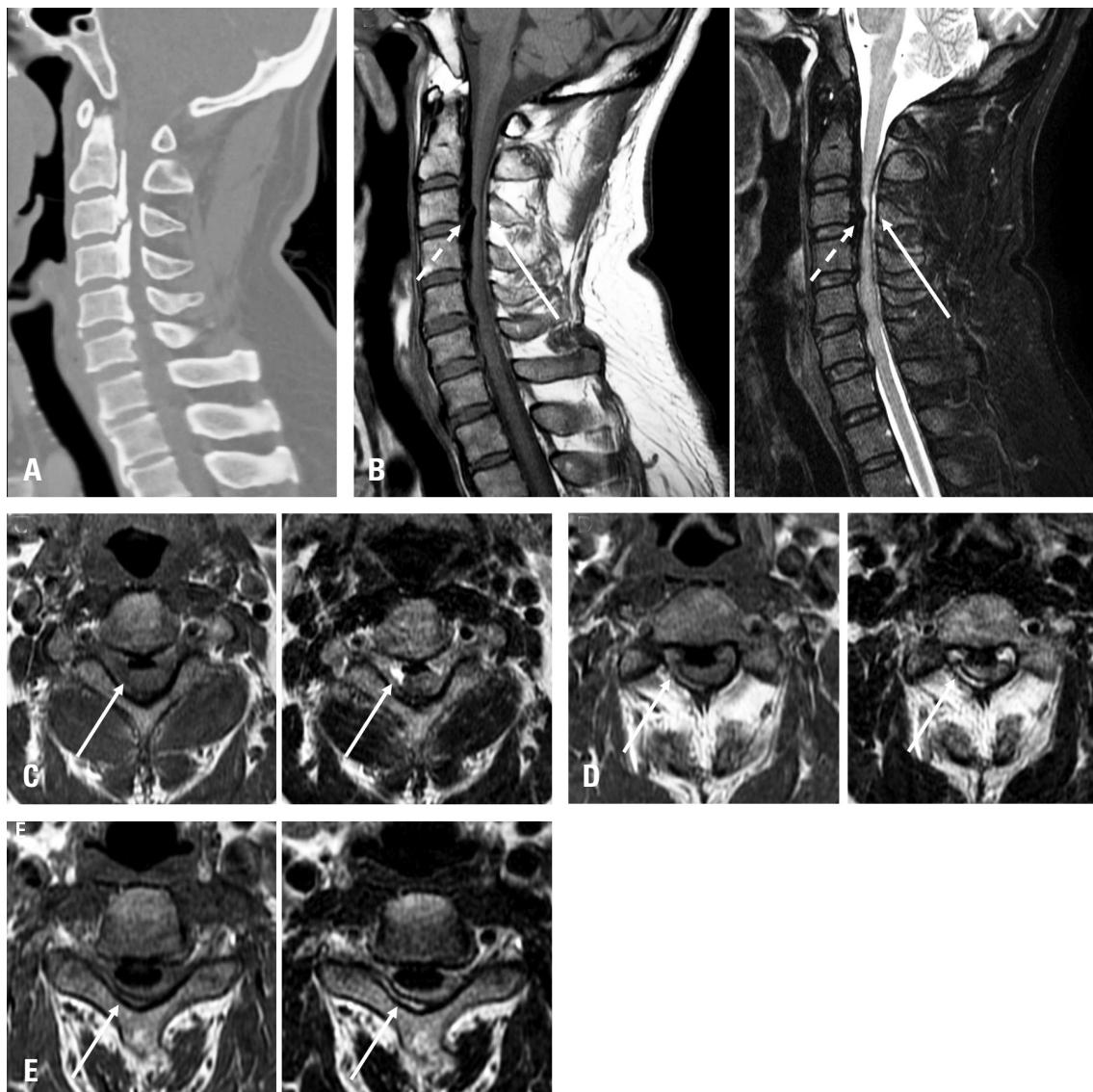


Fig. 1. **(A)** Preoperative computed tomography (CT): sagittal view. **(B)** Preoperative magnetic resonance imaging (MRI): T1-weighted image (left), T2-weighted image (right). Sagittal view, showing (pre-existing ossification of the posterior longitudinal ligament (white dotted arrow) and a cervical epidural hematoma (white arrow). **(C, D, E)** Preoperative MRI: T1 weighted image (left) and T2-weighted image (right). Axial views at the C2-3, C3, and C3-4 level, respectively. **(A)** On a sagittal view of computed tomography of the cervical spine, pre-existing ossification of the posterior longitudinal ligament is abutting the cord anteriorly from C2 to C6. **(B)** Posterior to the cord, there is an isointense/hyperintense signal lesion on T1/T2-weighted imaging, suggesting acute epidural hematoma compressing the cord. Cord signal change is also observed on T2-weighted imaging at the C3-4 level **(C, D, E)** On an axial view, the cervical cord is compressed by cervical epidural hematoma predominantly on the right posterior side at the C2-3, C3, and C3-4 levels, respectively.

formation. At 5 days postoperatively, after confirming the absence of factor VIII inhibitors by factor assay mentioned above, we decided to use recombinant factor VIII, instead.

However, at 10 days postoperatively, the coagulation lab for regular follow-up exhibited significant prolongation of the patient's aPTT to an undetectable level. Therefore, we immediately decided to re-administer Novoseven[®]. In spite of

a high titer of factor VIII inhibitor, again detected at 12 days postoperatively (55 Bethesda Unit [BU]), the patient exhibited no signs of re-bleeding or postoperative hematoma formation. Therefore, Novoseven[®] was administered only once or twice a day, just before rehabilitation treatment or other invasive procedures until the day of discharge.

Gradually, the patient's motor function was restored. At 5

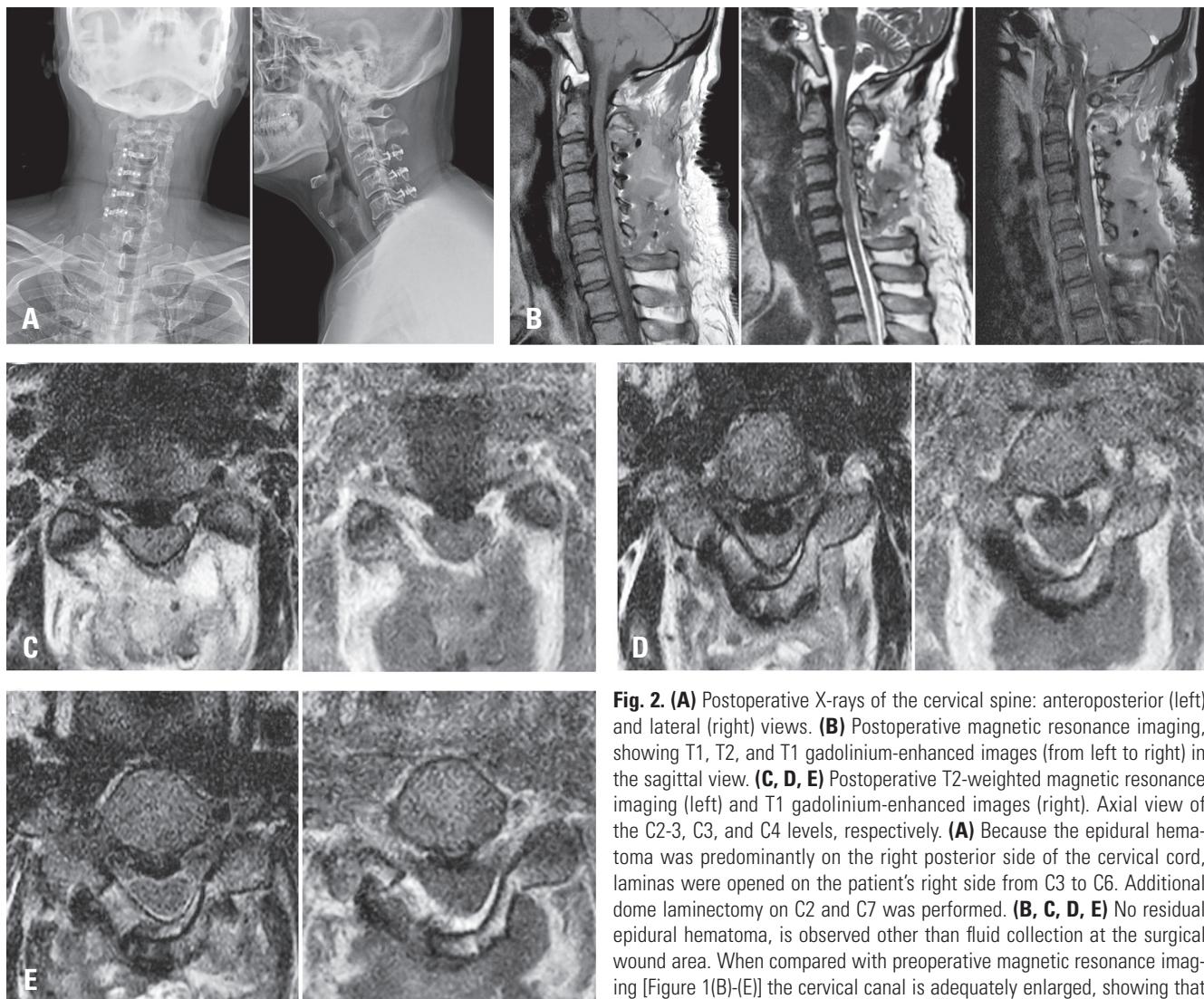


Fig. 2. **(A)** Postoperative X-rays of the cervical spine: anteroposterior (left) and lateral (right) views. **(B)** Postoperative magnetic resonance imaging, showing T1, T2, and T1 gadolinium-enhanced images (from left to right) in the sagittal view. **(C, D, E)** Postoperative T2-weighted magnetic resonance imaging (left) and T1 gadolinium-enhanced images (right). Axial view of the C2-3, C3, and C4 levels, respectively. **(A)** Because the epidural hematoma was predominantly on the right posterior side of the cervical cord, laminas were opened on the patient's right side from C3 to C6. Additional dome laminectomy on C2 and C7 was performed. **(B, C, D, E)** No residual epidural hematoma, is observed other than fluid collection at the surgical wound area. When compared with preoperative magnetic resonance imaging [Figure 1(B)-(E)] the cervical canal is adequately enlarged, showing that decompression was achieved.

days postoperatively, most of right upper extremity motors were restored to 3–4 motor grade. Moreover, the patient's right lower extremity motors were also restored to grade 3+~4. At 1 month postoperatively, on the day of discharge, the patient's motor grades on the right upper and lower extremities were nearly restored to 5, and his glove-like sensory deficits on both of his hands were nearly diminished (Table 1.)

No acute postoperative complications such as re-bleeding, hematoma formation and spinal cord injury were exhibited, and the patient had no neuropathic pain during hospitalization. However, residual hand clumsiness, ataxia when walking, and overstrain of urination/defecation were observed, and therefore the rehabilitation program for spinal cord injury patients was conducted during the hospital stay.

Table 1. Serial Changes of the Patient's Right Upper/Lower Extremity Motor

	Preoperative (PTD 3)	Postoperative (POD 5)	Discharge (POD 1 Month)
Shoulder Abduction (C5)	G2	G2	G4+
Elbow Flexion (C6)	G2	G4	G4+
Elbow Extension (C7)	G2	G2	G4+
Finger Flexion(C8)	G1	G3+	G4+
Finger Abduction (T1)	G1	G3+	G4+
Hip Flexion (L2)	U-C	U-C	U-C
Knee Extension (L3)	U-C	U-C	U-C
Ankle Dorsiflexion (L4)	G3+	G4	G4+
Hallux Extension (L5)	G3+	G4	G4+
Ankle Plantarflexion (S1)	G3+	G4	G4+

PTD: Post-Trauma Day, POD: Postoperative day, U-C: Uncheckable.

At 2 months postoperatively, the patient returned to the outpatient clinic and the patient's motor function on the right upper and lower extremities was still maintained to near-normal. He is still on a rehabilitation program for the restoration of residual neurologic deficits.

Discussion

Cervical epidural hematoma, though not often occurring, can be fatal and needs to be diagnosed and treated properly and promptly. Previous studies reported a few cases of cervical 'spontaneous' epidural hematoma. The most common symptoms were sudden, intense pain in the cervical/interscapular region and radiating pain to the upper extremity depending on the cord compression area. Other symptoms and signs include progression of neurological deficit below the level of cord compression, bowel/bladder disturbance, and gait instability.^{1,2)} Moreover, the cervical epidural hematoma can cause devastating results. Hiroaki Ono et al reported a spontaneous cervical epidural hematoma patient presenting with respiratory difficulty which needed urgent intubation.³⁾ Therefore, rapid decompression surgery is the treatment of choice. A. Matsumura et al. reported 7 cases of spontaneous epidural hematoma. In this report, 5 patients out of 7 underwent decompression surgery and 3 patients who underwent surgery within 14 hours of symptom onset recovered fully without any residual symptoms. In contrast, residual symptoms such as urinary dysfunction and motor weakness remained for 2 patients who underwent surgery after 24 hours.⁴⁾

However, our patient is quite different from ordinary cervical 'spontaneous' epidural hematoma cases. Our patient had a long treatment history of Hemophilia A with factor VIII inhibitors, and he had pre-existing canal stenosis due to cervical OPLL. Also, his epidural hematoma was caused by a minor traumatic injury (in this case – a neck and shoulder massage), and this aggravated cervical canal compromise and cord compression, which in turn leaded to our patient's neurological deficits. We believed lowering bleeding risk perioperatively was more important than just rapid decompression in this patient and therefore consultation on hematology expertise was mandatory.

The World Federation of Hemophilia (WFH) provides guidance for PwHA on factor VIII replacement, emphasizing the importance of achieving a peak target level of 80–100 IU/

dL and 50–80 IU/dL for major and minor surgery, respectively, and maintaining appropriate plasma factor levels.⁵⁾ However, PwHA with inhibitors requires long hospitalization and high cost due to the increased risk of postoperative bleeding. Inhibitors prevent the functioning of the coagulation cascade by neutralizing factor VIII. In case of low-titer inhibitors (<5 BU), hemostasis can still be achieved by administering higher doses of factor VIII to overcome the inhibitors. However, for high-titer inhibitors (>5BU), effective hemostasis is only obtained through the use of bypassing agents such as Novoseven® or factor VIII inhibitor bypassing activity (FEIBA® (Baxter AG, Vienna, Austria)).^{6,7)} Additionally, the exploration of new therapeutic agents, including non-factor hemostatic agents and rebalancing agents, is also expected to help reduce the risk of perioperative bleeding in the future.⁸⁾

To ensure optimal safety and minimize complications, our multidisciplinary team carefully planned the surgical approach, determining the appropriate method, timing, and selection of hemostatic agents and doses for perioperative management.

On plain X-ray and C-spine MRI, our 54-year-old, relatively young and active patient had no definite sign of structural instability, which might require posterior laminectomy and fusion operation. Hence, we selected laminoplasty operation as a primary option to preserve residual cervical motion. Of course, we also prepared for posterior laminectomy and fusion operation as a secondary option, if there was massive intraoperative bleeding or a high risk of postoperative hematoma formation. Nevertheless, owing to well-prepared preoperative bleeding risk management, blood loss during the surgery was minimal, and the epidural hematoma was well-evacuated. Therefore, we believe laminoplasty surgery was enough for our patient.

Yamamoto et al. reported two cases of spontaneous cervical epidural hematoma treated with hematoma evacuation and laminoplasty operation. Two patients in the report all improved markedly after the laminoplasty surgery and were discharged without definite complications.⁹⁾ Another case report by Iizuka, Yoichi et al, introduces laminoplasty operation preserving deep neck extensor muscles from C2 to T1 for a pediatric hemophilia A patient with spontaneous cervicothoracic epidural hematoma. The patient recovered from motor weakness and showed no kyphosis progression even 7 years after the surgery.¹⁰⁾

Moreover, given the patient's known high-titer inhibitors

and the need to prevent further cord compression before surgery, we administered Novoseven® (recombinant factor VII), which functions as a 'bypassing agent' of activating the extrinsic coagulation pathway.^{6,7)} Although the patient underwent operation 72 hours after the injury and onset of neurological deficits, we were able to minimize the EBL during the operation and achieve near-complete restoration of our patient's motor and sensory function. Activating the extrinsic pathway of PwHA with inhibitors is not a very novel strategy in hematology. Laura Villarreal-Martínez et al. reviewed 47 case reports of spinal epidural hematoma in patients with hemophilia from 1966 to 2020. 14 cases of PwHA with inhibitor titers ranging from 3 to 38 were found. Although in this report, there were only 3 cases who underwent surgery and the remaining 11 cases were on conservative treatment, all PwHA with high inhibitor titers (>5 BU) were administered Novoseven®, just like our patient.¹¹⁾ However, this strategy may not be very common knowledge to many orthopedic surgeons.

Conclusions

Before we proceed with spinal surgery on PwHA with inhibitors suffering spinal epidural hematoma, it is essential to know the exact problematic point on the coagulation cascade which is increasing perioperative bleeding risk. Selecting the appropriate recombinant factor agent and determining the optimal timing for surgery is essential for minimizing bleeding risk. Furthermore, maintaining appropriate factor replacement to prevent hematoma formation post-operatively is also crucial. We believe that this case report shows that not just 'rapid' surgery, but also 'safe' surgery is important in conducting surgery in PwHA with inhibitors and why the multidisciplinary team approach with hematology expertise for perioperative care is essential.

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혈액 응고 인자 VIII번 억제 인자를 가진 혈우병 A 환자에서 경도의 외상으로 발생한 경막외 혈종 및 척수 압박: 증례보고

오수현 · 신재원* · 안원기[†] · 서학성 · 김학선* · 문성환* · 석경수* · 박시영* · 이병호* · 권지원* · 이해원[†] · 한정우[†] · 한승민[†]

광명성애병원 정형외과, *연세대학교 의과대학 정형외과학교실, [†]연세의료원 연세암센터 소아과학교실 소아혈액증양내과

연구 계획: 증례 보고

목적: VIII번 혈액 응고 인자에 대한 억제 인자를 가진 혈우병 A 환자에서 경도의 경부 외상으로 발생한 경막외 혈종 사례의 소개

선행 연구문헌의 요약: 척추 경막외혈종은 드물지만 심각한 응급 질환이며, 혈우병 등 응고장애 또한 중요한 원인 중 하나이다.

대상 및 방법: VIII번 혈액 응고 인자에 억제 인자를 가진 54세 남성 혈우병 A 환자에서 확인된, 경추 후종인대골화증 및 추가적인 경막외 혈종에 따른 우측 상, 하지 마비소견에 대하여 경추 후궁 성형술을 통해 충분한 감압을 시행하였다. 혈액내과 입원 하 수술 전후 출혈 위험성을, 세밀한 관리를 통해 최소화하여 안전한 수술 시행이 가능하였다.

결과: 수술 후 환자는 신경학적 기능이 크게 회복되었으며, 특이 수술 후 합병증 없이 퇴원하였다.

결론: 혈우병 환자의 경막외 혈종의 치료에 있어 혈액내과 등 타과와의 다학제적 접근 및 단순히 '빠른' 수술 뿐 아니라 '안전한' 수술이 중요함을 알 수 있다.

색인 단어: 혈우병 A, 후종인대골화증, 경막외 혈종, 후궁성형술, 재조합 VIII번 혈액응고인자 보충

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서울특별시 서대문구 연세로 50-1, 연세대학교 의과대학 정형외과학교실

TEL: 02-2228-2192

FAX: 02-363-1139

E-mail: jaewuni@yuhs.ac

공동교신저자: 안원기

서울특별시 서대문구 연세로 50-1, 연세대학교 의과대학 소아과학교실

TEL: 02-2228-2050

FAX: 02-393-9118

E-mail: TOYRJ87@yuhs.ac