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Life-Threatening Tongue and Retropharyngeal Hemorrhage in a Patient with Hemophilia A with Inhibitors

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 71
Final Diagnosis: Hemophilia A
Symptoms: Dysarthria • dysphagia • dyspnea
Medication: —
Clinical Procedure: Cricothyrotomy • tracheotomy
Specialty: Hematology

Objective: Unusual clinical course

Background: Massive tongue hemorrhage in patients with hemophilia is a medical emergency because it can lead to airway obstruction. However, managing bleeding in patients with inhibitors is more difficult than in patients without inhibitors. We report a case of life-threatening massive tongue and retropharyngeal hematoma in a patient with hemophilia A who had inhibitors.

Case Report: The patient was a 71-year-old man with severe hemophilia A with high-responding inhibitors. He was admitted to our hospital with dysarthria and dysphagia secondary to a massive tongue hematoma. Although bypassing therapy was started immediately after admission, he rapidly developed an airway obstruction and cardiopulmonary arrest secondary to suffocation. Cardiopulmonary resuscitation and surgical cricothyrotomy were performed, which restored his pulse and breathing. On day 5 of hospitalization, he underwent tracheotomy under inhibitor-neutralizing therapy, and we began emicizumab on day 19 of hospitalization to prevent further bleeding events. He recovered and was transferred to another hospital for rehabilitation on day 64 of hospitalization.

Conclusions: Because tongue hematomas progress dramatically within a few days, prompt airway maintenance by tracheotomy under appropriate hemostatic therapy must be considered. Furthermore, emicizumab induction after primary hemostasis prevents further bleeding. We suggest that initiating emicizumab therapy is a good choice to prevent further bleeding after critical bleeding events if the patient has not received the drug previously.

MeSH Keywords: Asphyxia • Cardiopulmonary Resuscitation • Heart Arrest • Hemophilia A • Tracheotomy

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Background

Replacing the deficient coagulation factor to prevent bleeding events is the mainstay of hemophilia treatment. However, repeated infusions of the coagulation factor sometimes result in the production of alloantibodies ("inhibitors") that act against the factor [1]. Once bleeding occurs in a patient with inhibitors, even though the patient might receive bypassing agents such as recombinant activated factor VII (rFVIIa), activated prothrombin complex concentrate (APCC), or plasma-derived activated factor VII and factor X to achieve hemostasis, bleeding is difficult to manage and might be severe and lethal [2]. In particular, airway bleeding is a serious emergency for hemophilia management, and requires the prompt initiation of hemostatic therapy and the decision to perform appropriate airway control, such as tracheal intubation and tracheotomy.

We report a case of life-threatening massive tongue and retropharyngeal hematoma in a patient with hemophilia A with inhibitors. Although he rapidly developed an airway obstruction and cardiopulmonary arrest secondary to suffocation, we successfully managed the massive bleeding and saved the patient's life.

Case Report

The patient was a 71-year-old man with severe hemophilia A with high-responding inhibitors who had been followed regularly at our hospital. He had undergone several invasive procedures, including transurethral resection for a bladder tumor and transcatheter arterial chemoembolization for hepatocellular carcinoma. His bleeding had been managed using bypassing agents and inhibitor-neutralizing therapy. He was considered for treatment with emicizumab, a novel humanized bispecific antibody, for bleeding prophylaxis, but had not yet begun this therapy. He was admitted to our hospital with dysarthria and dysphagia secondary to tongue hematoma, and although he was unaware of any tongue injury, his wife noticed a small hematoma on his tongue the day before his admission. On initial examination, his temperature was 36.3°C, with a blood pressure of 152/98 mmHg, pulse of 70 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 96% on room air. His tongue was extremely swollen, dark purple in color, and protruded from his mouth (Figure 1A). Stridor was heard in his lungs during chest auscultation, but the rest of the examination showed no unusual changes. Laboratory testing revealed the following: hemoglobin: 13.0 g/dL; activated partial-thromboplastin time (APTT): 126.0 seconds (reference range: <37.0 seconds); factor VIII (FVIII): <1.0% (reference range: 78.0–165.0%); and factor VIII inhibitor titer: 2.5 Bethesda Units (BU)/mL. Contrast-enhanced computed tomography of the neck and chest revealed massive tongue hematoma with the hematoma expanding into the left submandibular to pharyngolaryngeal areas (Figure 1B). Immediately after admission, bypassing therapy with rFVIIa (NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) was started at 90 µg/kg every 2 hours. After the third administration of rFVIIa, he developed dyspnea, and his oxygen saturation dropped to 92% on room air. We determined that his bleeding and hematoma were worsening, and decided to perform tracheal intubation. After transferring the patient to the intensive care unit, an anesthesiologist tried to perform intubation; however, during intubation using an airway scope and a transnasal bronchoscope, the patient rapidly developed an airway obstruction and cardiac arrest. Cardiopulmonary resuscitation was initiated immediately followed by surgical cricothyrotomy, and the patient's pulse and breathing were restored within 10 minutes. Because of the cricothyrotomy, bleeding from the wound continued, and otolaryngologists tried to stop the bleeding for several hours. However, because the bleeding did not stop despite 2 administrations of rFVIIa during the procedure, we changed the bypassing agent to APCC (FEIBA®; Shire, Dublin, Ireland). After administering APCC at 100 U/kg, the bleeding stopped; however, the patient again developed cardiopulmonary arrest because of coagulated blood within the trachea. Cardiopulmonary resuscitation was initiated again, and pulse and breathing were restored 9 minutes later. Subsequently, his respirations stabilized, and active bleeding stopped. We continued intensive care and APCC infusion at 70 U/kg every 8 hours, and on day 5 of hospitalization, we planned to perform tracheotomy. To prevent bleeding, we initiated inhibitor-neutralizing therapy using a calculated dose of recombinant factor VIII (rFVIII; Advate®; Shire). We injected a bolus dose of rFVIII 1 hour before the procedure, followed by continuous infusion of rFVIII. The operation was completed safely without massive bleeding. A summary of the patient's management during the first 5 days in hospital is shown in Figure 2. On day 9 of hospitalization, we stopped the rFVIII because the patient's inhibitor titer had increased sharply to 219.4 BU/mL and his APTT was 112.3 seconds. rFVIIa was administered again, then gradually reduced, and was terminated on day 16 of hospitalization because the bleeding had completely stopped. His tongue hematoma was most swollen on day 5 of hospitalization (Figure 1C) and gradually improved thereafter (Figure 1D). We started emicizumab (Hemlibra®; Chugai Pharmaceutical, Tokyo, Japan) on day 19 of hospitalization to prevent further bleeding events; thereafter, his APTT normalized and he showed no further bleeding tendency. Although it took several days to discharge the patient from hospital because he had developed pneumothorax and pneumonia after the cardiopulmonary arrest, he had recovered and was transferred to another hospital for rehabilitation on day 64 of hospitalization.

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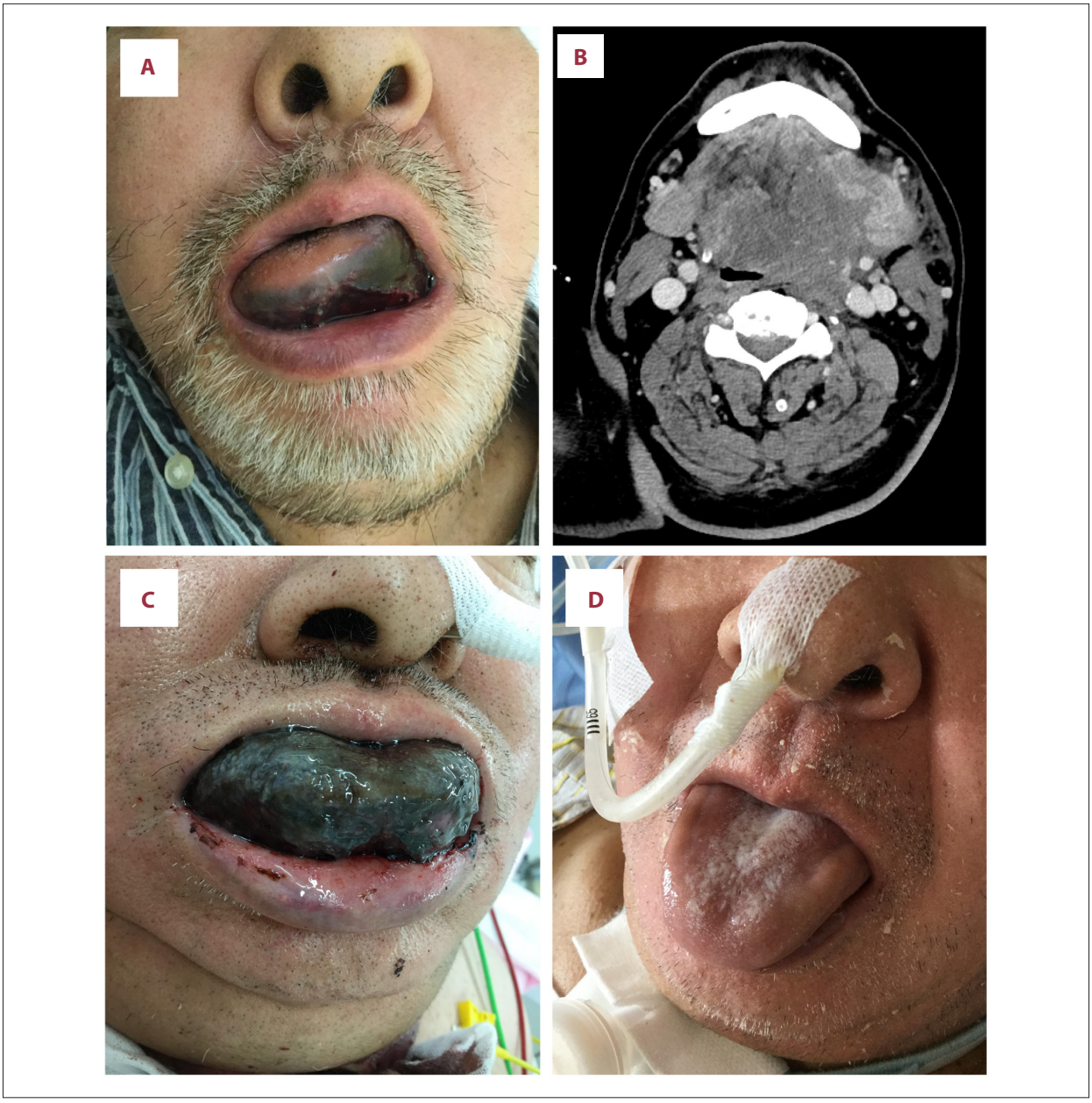

Figure 1. Images of our patient's tongue and retropharyngeal hemorrhage. (**A**) The massive tongue hematoma on admission. (**B**) Contrast-enhanced computed tomographic image at the level of the third cervical vertebra showing retropharyngeal hemorrhage and airway stenosis. (**C**) The tongue hematoma extended dramatically on day 5 of hospitalization. (**D**) The tongue hematoma resolved completely by the time of discharge from hospital.

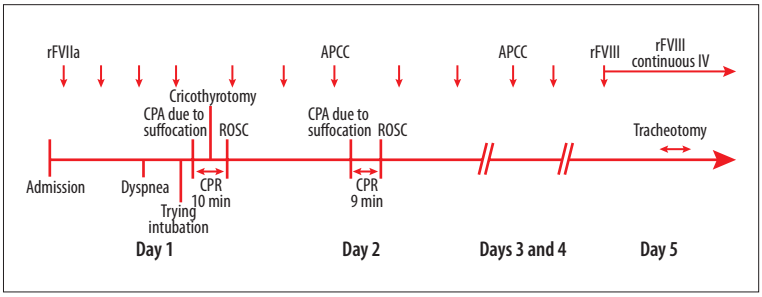

Figure 2. Summary of the patient's management for the first 5 days in hospital. APCC – activated prothrombin complex concentrate; CPA – cardiopulmonary arrest; CPR – cardiopulmonary resuscitation; IV – intravenous; rFVIIIa – recombinant activated factor VIII; ROSC – return of spontaneous circulation.

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Discussion

Airway hemorrhage in patients with hemophilia is not considered major bleeding, but is a medical emergency because it can lead to airway obstruction [3]. One of the most important points in hemophilia management is maintaining the airway under appropriate hemostatic therapy. Ten case reports in the last 20 years discuss airway obstruction secondary to tongue and/or retropharyngeal hemorrhage in patients with hemophilia who required airway maintenance by intubation or tracheotomy [4–13]. Five of the 10 patients required tracheotomy, 4 of the 10 patients suffered failed intubation and required emergency cricothyrotomy, and 1 of the 10 patients died. Our report describes an extremely rare case of a patient who fully recovered from cardiopulmonary arrest secondary to suffocation. Because the usual intubation techniques such as oral and nasal insertion are extremely difficult to perform in a patient with massive airway hemorrhage, one should not hesitate to perform cricothyrotomy or tracheotomy. Hemophilia can also lead to airway obstruction secondary to tonsillitis and epistaxis [14,15]. If there is even a slight possibility of airway obstruction, hospitalization and evaluation by a specialist are essential [3].

The management of bleeding in patients with inhibitors is more difficult than in patients not with inhibitors, and the choice of treatment product should be based on the inhibitor titer and the patient's clinical records related to anamnestic responses to the product [3]. Patients with high-responding inhibitors but low titers (<5 BU/mL), such as in our patient, should be treated with bypassing agents or inhibitor-neutralizing therapy. Because an anamnestic response occurs from 4–7 days after neutralizing therapy, it is necessary to monitor FVIII activity and APTT frequently and to change the therapy to a bypassing agent with appropriate timing.

Bypassing agents, such as rFVIIa and APCC, provide hemostasis by activating the extrinsic pathway without using FVIII. The ability of these 2 agents to treat bleeding in patients with hemophilia A and inhibitors is similar [16]. We chose to use rFVIIa first in our patient because this agent was effective in his previous bleeding events; however, it was not effective during the event described in this report. Research suggests that if a bypassing agent does not provide adequate hemostasis, changing to another bypassing agent may be effective [17,18]. Although hemostasis was achieved when we changed from rFVIIa to APCC during airway bleeding after cricothyrotomy, the clot in the trachea led to a second suffocation episode and cardiopulmonary arrest. Because the hemostatic effect of bypassing agents is difficult to predict, it is important to be aware of over-coagulation and clot formation in patients experiencing airway bleeding.

We began emicizumab therapy in our patient after the bleeding had stopped. Emicizumab is a humanized bispecific antibody that binds to and bridges activated factor IX and factor X, thereby acting as an FVIII-mimetic agent [19]. This novel agent recently became available for bleeding prophylaxis in patients with hemophilia with inhibitors as an alternative to rFVIIa and APCC [20]. Because several weeks are needed to provide efficient hemostatic activity after initiating emicizumab, this agent is used for bleeding prophylaxis rather than for hemostasis in acute bleeding [21]. When a patient with inhibitors who has not started emicizumab develops severe hemorrhage, we recommend administering a bypassing agent or neutralizing therapy followed by emicizumab to control bleeding. Indeed, we performed tracheal tube replacement and rehabilitation safely by administering emicizumab. To the best of our knowledge, this is the first report describing severe hemophilia in a patient with inhibitors who underwent successful treatment with early introduction of emicizumab after life-threatening airway bleeding.

Conclusions

We reported our experience treating a patient with hemophilia A with inhibitors who developed an airway obstruction, suffocation, and cardiopulmonary arrest secondary to a rapidly deteriorating massive tongue and retropharyngeal hematoma. Because a tongue hematoma progresses dramatically within a few days, promptly maintaining the airway by tracheotomy under appropriate hemostatic therapy must be considered, and hematologists should cooperate closely with anesthesiologists and otolaryngologists. We recommend early emicizumab administration after hemostasis to maintain hemostasis and prevent further bleeding.

Department and institution where the work was done

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Conflicts of interest and financial support

H. Wada received speaking fees from Alexion and IL Japan, outside of the submitted work. N. Katayama received honoraria from Chugai Pharmaceutical and research support from Kyowa Hakko Kirin, Ono Pharmaceutical, Takeda Pharmaceutical, and Astellas Pharma, outside of the submitted work.

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