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CASE REPORT

Spontaneous multilevel airway haemorrhage in acquired haemophilia A

Anna See[1] · Siti Radhziah Sudirman[1] · Xin Yong Huang[1]

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Abstract
Background Acquired haemophilia A is caused by the development of an autoantibody to factor VIII in a person with previously normal haemostasis. The most common clinical presentation in hereditary haemophilia is intra-articular bleeding. In contrast, acquired haemophilia more commonly presents with skin, soft tissue and mucosal haemorrhages.
Methods We present a case of a patient with idiopathic acquired haemophilia A, whose initial presentation was that of spontaneous submental and submandibular haematoma which rapidly progressed to involve multiple sites in the airway, ultimately necessitating an emergent tracheotomy. In view of the extremely rare occurrence of this phenomenon, a systematic review and summary of all previously reported cases is also presented.
Results The diagnostic and management dilemmas encountered in this case are presented from an otolaryngologist's perspective.
Conclusions Otolaryngologists' awareness of underlying haematological pathologies and their natural course of disease in cases of severe airway haemorrhage is of paramount importance in anticipating evolving issues in management of these patients.

Keywords Haemophilia · Airway · Haemorrhage · Haematoma · Tracheostomy

✉ Xin Yong Huang
hxy1976@yahoo.com

[1] Department of Otorhinolaryngology - Head & Neck Surgery, Changi General Hospital, Singapore, Singapore

Introduction

Hereditary haemophilia A is an X-linked, recessive disorder caused by the deficiency of functional plasma clotting factor VIII. Non-hereditary or acquired haemophilia A is caused by the development of an autoantibody to factor VIII in a person with previously normal haemostasis. With an estimated incidence of 1 case per 1 million per year, acquired haemophilia A is extremely rare [1]. However, with a disproportionately high mortality rate of up to 22 %, usually attributed to uncontrolled haemorrhage, it poses as a demanding clinical challenge [2]. The most common presentation of hereditary haemophilia is intra-articular bleeding whilst that of acquired haemophilia is haemorrhage in skin, soft tissue and mucosae. In this article, we report a case of a patient with idiopathic acquired haemophilia A whose initial presentation was that of submental and submandibular haematoma which rapidly progressed to involve multiple sites in the airway, ultimately necessitating an emergent tracheotomy.

Case report

A 61-year-old Chinese gentleman presented with an acute onset of painful left neck swelling and hoarseness. Previously well, his neck swelling had developed within hours. He denied any associated fever or symptoms of upper respiratory tract infection but reported increasing respiratory distress and dysphagia. Apart from hypertension and hyperlipidaemia, the patient had a significant history of ischaemic heart disease for which he was on daily aspirin use. He had no known family or personal history of bleeding diatheses.

Physical examination revealed a tense submental swelling with lateral extension to the left submandibular region, measuring approximately 5 cm by 3 cm. The floor of mouth was raised with mucosal bruising. The patient was dyspnoeic and hoarse but was not stridorous. Nasoendoscopy revealed posterior displacement of the base of tongue in the oropharynx, mild medialisation of the left parapharyngeal wall, a haemorrhagic left true vocal fold and oedematous left arytenoid and epiglottis. Lateral neck X-ray revealed marked soft tissue swelling in the submental region (Fig. 1). Urgent computed tomography (CT) of the neck was performed, demonstrating soft tissue thickening at the left submandibular region extending into the left parapharyngeal space and left oropharynx (Fig. 2). Significant local mass effect on the oro- and hypo- pharynx with right lateral displacement was also noted.

Biochemical and haematological investigations revealed normal haemoglobin and platelet count levels (11.9 g per decilitre and 353,000 platelets per microliter respectively). Inflammatory markers were only mildly elevated—white cell count at 10,900 per microliter and C-reactive protein at 23.5 mg per litre, suggesting that the aetiology was unlikely infectious, such as a submental or submandibular abscess. Notably, the coagulation profile was markedly deranged with an activated partial thromboplastin time (aPTT) of 60.9 s (normal range 24.0–34.0 s). Prothrombin time was, however, normal at 10.8 s. The impending airway compromise prompted immediate otolaryngological involvement. A technically difficult awake fibreoptic nasal intubation was performed. Incision and drainage of his neck swelling, with evacuation of the floor of mouth hematoma via a submental skin incision was then carried out. Intra-operatively, a communicating submental and left submandibular space haematoma was noted. No pus or inflammatory debris was encountered. Instead, generalised bruising of the platysmal and mylohyoid muscles was noted. Upon evacuation of the haematoma, the floor of mouth swelling markedly reduced. Post-operatively, the patient remained intubated.

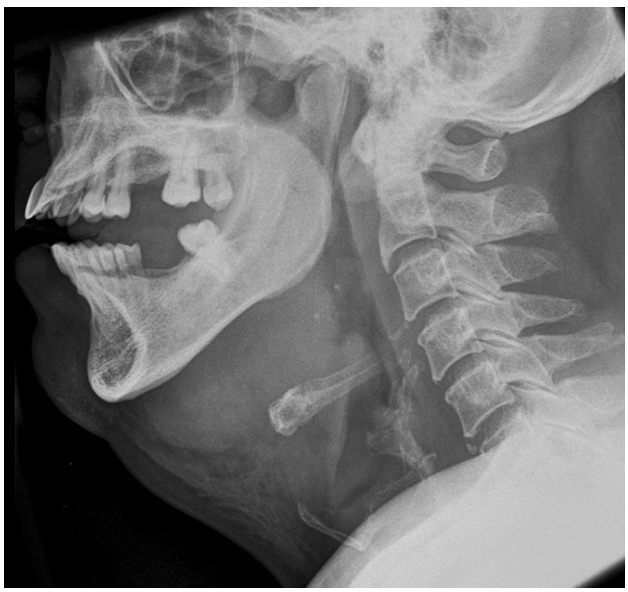

Fig. 1 Lateral neck X-ray demonstrating large submental and submandibular soft tissue swelling

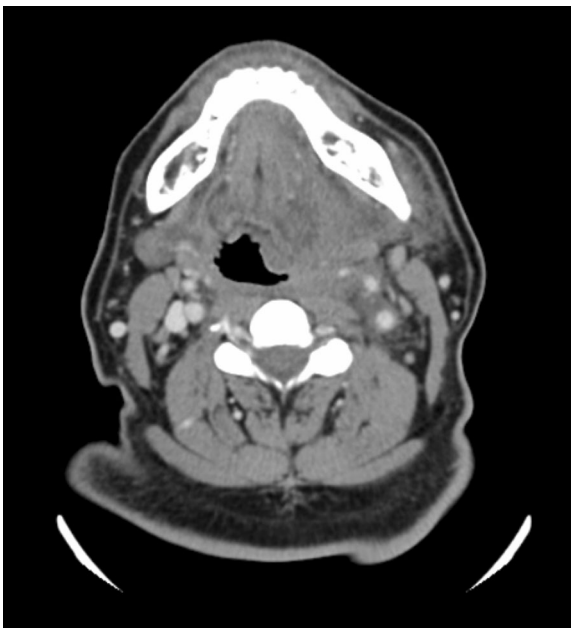

Fig. 2 CT neck demonstrating soft tissue thickening at the left submandibular region extending into the left parapharyngeal space and left oropharynx

Thought initially to be caused by aspirin use, his isolated deranged aPTT level failed to normalise despite suspension of aspirin, prompting further haematological work-up. Subsequent haematological investigations revealed poor correctability of aPTT levels with a 50:50 mixing study. Factor VIII assay was low and factor VIII circulating inhibitor assay was positive with a normal factor IX and fibrinogen assay. Lupus anti-coagulant was negative. These results confirmed a diagnosis of acquired haemophilia A.

The patient was started on factor eight inhibitor bypassing activator (FEIBA), prednisolone and cyclophosphamide. On post-operative day 2, increasing ventilator pressures via the endotracheal tube was noted. Endoscopic examination revealed a superiorly displaced endotracheal tube caused by generalised laryngeal swelling secondary to hematoma progression. An emergent tracheotomy under local anaesthesia was performed and the airway re-secured. Continual and aggressive medical treatment of his underlying haematological disorder persisted. A comprehensive work-up revealed no identifiable cause and he was eventually diagnosed with idiopathic

acquired haemophilia A. There were no further airway complications and the patient was successfully decannulated on post-operative day 22.

Discussion

Acquired haemophilia A is a rare but potentially life-threatening bleeding diathesis caused by the development of autoantibodies or inhibitors directed against factor VIII, an essential component of the coagulation cascade. In contrast to patients with hereditary haemophilia, acquired haemophilia is much rarer, with an estimated yearly incidence of 15 % of all haemophilia cases [3]. Acquired haemophiliacs do not have a personal or family history of bleeding episodes. Associations have been found with pregnancy, autoimmune disease, and undiagnosed malignancies. However, the large majority of cases are often idiopathic [4]. In hereditary haemophiliacs, intra-articular bleeding is typically the first manifestation of the disease [5]. In contrast, acquired haemophilia presents with skin, soft tissue and mucosal haemorrhages [3]. The reason for the difference in bleeding features is, however, not well-elucidated. Acquired haemophilia should be suspected when a patient with no prior of bleeding diathesis presents with unexplained bleeding and prolonged aPTT which is not correctable by mixing studies, suggesting the presence of an inhibitor.

Our patient had severe spontaneous multilevel airway haemorrhage resulting in airway compromise. His condition initially masqueraded as a submental and submandibular haematoma which seemingly resolved with evacuation. However, progression of the haematoma along the parapharyngeal space and larynx resulted in tube dislodgement, necessitating an emergent tracheotomy. This posed as both a diagnostic and management otolaryngological dilemma. Our case illustrates the rare but potentially lethal bleeding complication of haemophilia in a critical anatomical area. Additionally, prompt haematological involvement and early elucidation of the underlying diagnosis is of paramount importance.

The acute treatment of bleeding episodes depends on the inhibitor titers. Patients with a low titer of inhibitor [<5 Bethesda units (BU)/mL] can be treated with concentrates of human factor VIII [6, 7]. In these patients, desmopressin has also been shown to be a reasonable alternative [8]. When inhibitor titers are high (>5 BU/mL), heterologous factor VIII and bypassing agents should be administered [9, 10]. In rare and extreme cases where intractable bleeding and high titers of inhibitor are present, therapeutic plasmapheresis, or immunoadsorption may be used to rapidly reduce the circulating load of inhibitors prior to factor concentrate treatment [11].

Immunosuppression is often required for long-term eradication of the inhibiting autoantibodies, especially in patients with idiopathic acquired haemophilia A where no underlying pathology may be found and removed. The immunosuppressive agents include corticosteroids (most commonly prednisone), cyclophosphamide, azathioprine, 6-mercaptopurine, and vincristine [3, 4, 12]. Immune treatment protocols, usually consisting of a combination of human factor VIII, cyclophosphamide, and methylprednisolone have shown to be highly effective in eradicating

Table 1 A summary of all cases of spontaneous airway haemorrhage in haemophilia A reported in English literature

Serial no. and year of report	Site of spontaneous airway haemorrhage	Treatment to secure airway	Recovery with successful extubation or decannulation	References
1. 1950	Retropharyngeal space	Intubation	Yes	[15]
2. 1953	Submandibular, submental and buccal spaces	Intubation	Yes	[16]
3. 1980	Upper airway	Intubation	Yes	[17]
4. 1981	Retropharyngeal space	Nil	Yes	[18]
5. 2007	Retropharyngeal space	Intubation followed by tracheotomy	Yes	[19]
6. 2010	Epiglottis	Nil (close airway monitoring in intensive care unit)	Yes	[14]
7. 2011	Submandibular and sublingual spaces	Intubation	No—demised after 96 h	[20]
8. 2013	Base of tongue	Failed intubation, followed by emergency cricothyroidotomy and tracheotomy	Yes	[21]
9. 2015	Retropharyngeal space	Nil	Yes	[22]
10. 2016	Submandibular, submental, retropharyngeal and parapharyngeal spaces	Intubation, followed by emergency tracheotomy	Yes	Current case

factor VIII autoantibodies in patients presenting with severe bleeding [13].

An extensive search on PubMed revealed that spontaneous airway haemorrhage in acquired haemophilia A is a rare occurrence and is usually associated with high morbidity. Thus, we performed a systematic review of all cases of spontaneous airway haemorrhage in haemophilia A to characterize this rare group of patients. An English literature search on PubMed performed using the terms 'haemophilia', 'airway', 'haemorrhage', 'haematoma', "bleeding", 'tracheotomy' are summarized in Table 1 [14–22].

The surgeon's role in the care of a bleeding haemophiliac patient consists of controlling the bleeding source and establishing an airway. While localised airway compromise secondary to spontaneous epiglottic haematoma in hereditary haemophilia A has been reported in English literature, cases of spontaneous multilevel airway haemorrhage secondary to haemophilia A necessitating emergent tracheotomy, such as ours, is extremely rare [14]. Otolaryngologists' awareness of underlying haematological pathologies and their natural course of disease in cases of severe airway haemorrhage is of paramount importance in anticipating evolving issues in management of these patients. Endotracheal intubation may be attempted for early and rapid securement of the airway but regular assessment must be performed due to the progressive and dynamic nature of the haematological illness. Prophylactic tracheotomy should also be considered in future cases to definitively secure the airway, especially if there is a suspicion for further progression of haematoma which could result in issues with endotracheal intubation management.

Compliance with ethical standards

Funding This study did not receive any funding.

Conflict of interest All authors of this manuscript declare no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from the patient in this case report, with permission to discuss his case history and publication of his scans.

References

1. Shetty S, Bhave M, Ghosh K (2011) Acquired hemophilia A: diagnosis, aetiology, clinical spectrum and treatment options. Autoimmun Rev 10:311–316
2. Yee TT, Pasi KJ, Lilley PA, Lee CA (1999) Factor VIII inhibitors in haemophiliacs: a single-centre experience over 34 years, 1964–1997. Br J Haematol 104:909–914
3. Franchini M, Gandini G, Di Paolantonio T, Mariani G (2005) Acquired hemophilia A: a concise review. Am J Hematol 80:55–63
4. Hay CR (1998) Acquired haemophilia. Baillieres Clin Haematol 11:287–303
5. Bogdan C, Strauss M, Ratnoff O (1994) Airway obstruction in hemophilia (factor VIII deficiency): a 28-year institutional review. Laryngoscope 104:789–794
6. Boggio LN, Green D (2001) Acquired hemophilia. Rev Clin Exp Hematol 5:389–404
7. Kessler CM (2000) Acquired factor VIII autoantibody inhibitors: current concept and potential therapeutic strategies for the future. Haematologica 85(Suppl):57–63
8. Gandini G, Franchini M, Manzato F, Lippi G, Aprili G (1999) A successful combination of prednisone, high-dose intravenous immunoglobulin and desmopressin in the treatment of acquired haemophilia A with high-titer inhibitor. Haematologica 84:1054
9. Hay CR (2000) Porcine factor VIII: past, present and future. Haematologica 85(Suppl):21–25
10. Hilgartner MW, Knatterud GL, FEIBA Study Group (1983) The use of factor eight inhibitor by-passing activity (FEIBA Immuno) product for treatment of bleeding episodes in hemophiliacs with inhibitors. Blood 61:36–40
11. Jansen M, Schmaldienst S, Banyai S, Quehenberger P, Pabinger I, Derfler K (2001) Treatment of coagulation inhibitors with extracorporeal immunoadsorption (Ig-Therasorb). Br J Haematol 112:91–97
12. Petrovic M, Derom E, Baele G (2000) Cyclosporine treatment of acquired hemophilia due to factor VIII antibodies. Haematologica 85:895–896
13. Nemes L, Pitlik E (2000) New protocol for immune tolerance induction in acquired hemophilia. Haematologica 85:64–68
14. Hirshoren N, Varon D, Weinberger JM, Gross M (2010) Airway obstruction and hemophilia-A: epiglottis hematoma. Laryngoscope 120:1428–1429
15. Boyd WH (1950) Respiratory obstruction in hemophilia; recovery after intubation. Lancet 1(6599):302
16. Macdonald AC, Robson JG, Wapshaw H (1953) Haemophilia with respiratory obstruction. Br Med J 1(4820):1144–1146
17. Stanievich JF, Marshak G, Stool SE (1980) Airway obstruction in a hemophiliac child. Ann Otol Rhinol Laryngol 89(6 Pt 1):572–573
18. Markowitz RI, Mendel JB (1981) Retropharyngeal bleeding in haemophilia. Br J Radiol 54(642):521–523
19. Harper M, Obolensky L, Roberts P, Mercer M (2007) A case of acute upper and lower airway obstruction due to retropharyngeal haemorrhage secondary to acquired haemophilia A. Anaesthesia 62(6):627–630
20. Al-Hilou A, Reid J, Kelly R, Ong TK (2011) Acquired factor VIII deficiency presenting as a floor of the mouth swelling. BMJ Case Rep 4:2011
21. Kelly ME, Martlew V, Thachil J (2013) A 'Bloody' hot stew. QJM 106(1):67–68
22. López-Sánchez I, Alba-García J, Vázquez-Romero C, Armengot-Carceller M (2015) Acquired hemophilia A simulating retropharyngeal abscess: importance of differential diagnosis of neck masses before surgery. Int J Otolaryngol Head Neck Surg 4:282–285