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Acquired Hemophilia A induced by Clopidogrel: A Case Report

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ABSTRACT

Introduction: Acquired hemophilia A (AHA) is a rare bleeding disorder caused by intervention of factor VIII by autoantibody. Most AHA cases arise from underlying medical conditions such as autoimmune disorders, cancers, drug/allergic reaction, with 50% cases are idiopathic.
Case Presentation: 60-year old Asian male complained weakness worsened in the last two days accompanied by fatigue and pallor. Patients has history of percutaneous coronary intervention in proximal and distal of left anterior descending artery. Patient's aPTT mixed with normal plasma before incubation is 41 seconds and after incubation became 59 seconds, it can be concluded that patient has time dependent FVIII antibody and his diagnosis became Acquired Hemophilia A. Methylprednisolone 0,5 mg/kg/day was added to his treatment following his diagnosis
Discussion and Conclusions : Drug induced AHA can be caused by several medications, including antibiotics (penicillin, sulfonamides, chloramphenicol), anticonvulsants (phenytoin), methyldopa, interferon-α, clopidogrel, fludarabine . In this case, patient has a history of percutaneus intervention with routine consumption of clopidogrel and aspirin for 3 months. Clopidogrel therapy for 3 months is suspected as a cause of AHA emergence in this patient. Short-term, high-dose immunosuppressive treatment with oral prednisone (1 mg/kg for 10 days, 0.5 mg/kg for 20 days, and 0.25 mg/kg for 15 days) can reduce the incidence of angiographic restenosis with minor secondary effects such as gastric pain, water and salt retention, and worsened hypertension in nearly 10% patients.

Keywords: Acquired Hemophilia; Clopidogrel; Coronary Artery Disesase

ABSTRAK

Pendahuluan : Acquired hemophilia A (AHA) adalah kelainan perdarahan langka yang disebabkan oleh intervensi faktor VIII oleh autoantibodi. Sebagian besar kasus AHA timbul dari kondisi medis yang mendasari seperti gangguan autoimun, kanker, reaksi alergi / obat, dengan 50% kasus bersifat idiopatik.
Persentasi Kasus : Laki-laki berusia 60 tahun mengeluh lemas memberat dalam dua hari terakhir disertai kelelahan dan pucat. Pasien memiliki riwayat *percutaneuos coronary intervention* di bagian proksimal dan distal arteri desenden anterior kiri. APTT pasien *mixed* dengan plasma normal sebelum inkubasi adalah 41 detik dan setelah inkubasi menjadi 59 detik, dapat disimpulkan bahwa pasien memiliki antibodi FVIII yang tergantung waktu dan diagnosisnya menjadi Acquired Hemophilia A. Methylprednisolone 0,5 mg / kg / hari ditambahkan pada pengobatan setelah diagnosis AHA tegak.

Diskusi dan Kesimpulan : AHA yang diinduksi obat dapat disebabkan oleh beberapa obat, termasuk antibiotik (penisilin, sulfonamida, kloramfenikol), antikonvulsan (fenitoin), metildopa, interferon-α, clopidogrel, fludarabine. Dalam kasus ini, pasien memiliki riwayat *percutaneous coronary intervention* dengan konsumsi rutin clopidogrel dan aspirin selama 3 bulan. Terapi klopidogrel selama 3 bulan diduga sebagai penyebab munculnya AHA pada pasien tersebut. Pengobatan imunosupresif dosis tinggi jangka pendek dengan prednison oral (1 mg / kg selama 10 hari, 0,5 mg / kg selama 20 hari, dan 0,25 mg / kg selama 15 hari) dapat mengurangi kejadian restenosis angiografik dengan efek sekunder minor seperti sebagai nyeri lambung, retensi air dan garam, dan hipertensi yang memburuk pada hampir 10% pasien**.**

Kata Kunci : Clopidogrel; Hemofilia yang didapat; Penyakit Jantung Koroner

INTRODUCTION

Acquired hemophilia A (AHA) is a rare bleeding disorder caused by intervention of factor VIII by autoantibody. Immunoglobulin G antibodies bind to the surface of factor VIII molecule, impairing blood coagulation process which may result in life-threatening hemorrhage if not treated promptly[1]. Most AHA cases arise from underlying medical conditions such as autoimmune disorders, cancers, drug/allergic reaction, with 50% cases are idiopathic. AHA prevalence increases with age from 0.045 per million per year in children <16 years to 14.7 per million per year in adult >85 years[2]. Clinical presentation of AHA includes spontaneous or provoked bleeding, usually in mucocutaneous sites or soft tissues, in a person with negative history of coagulopathy[3]. Bleeding associated with AHA may appear as spontaneous subcutaneous hematomas, extensive bruising, muscle bleeding, hematuria, epistaxis, gastrointestinal bleeding, and intracranial hemorrhage[4]. Lab study will show prolonged activated partial thromboplastin time (aPTT). Further diagnosis requires coagulation and mixing studies[5]. Management of AHA focuses on bleeding control, immunosuppression to eliminate antibodies, and treating underlying medical condition[6].

CASE PRESENTATION

A 60-year old Asian male complained weakness worsened in the last two days accompanied by fatigue and pallor. In the past week, his right elbow became swollen followed by pain and limited range of motion. There are no mucosal bleeding signs such as melena, epistaxis, and bleeding gums. He was diagnosed with Hemophilia A since two months ago and currently under routine treatment of antihemophilic factor Koate 3000 IU per week. However, the bleeding on his elbow persisted after 2 months despite the treatment he received. He is also under therapy of Candesartan 1x16 mg, Diltilazem 1x100 mg, Furosemide 1x40 mg for his hypertension. Patients has history CAD (Coronary Artery Disease) in three VD (Vessel Disease) with PCI (Percutaneous Coronary Intervention) and one DES (Drugs Eluting Stent) in proximal and distal of left anterior descending artery.

Musculoskeletal ultrasound on his right elbow revealed joint effusion with internal echo leading to hemarthrosis. Laboratory blood test on admission showed low hemoglobin (4.4 g/dL); low erythrocyte (1.67 x 10^6/mL); however, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were in normal range (86.2 fL and 26.3 pg). Albumin was low (2.95 g/L); activated partial thromboplastin time (aPTT) was prolonged (102.2 seconds); and international normalized ratio (INR) was high (1.36). Patient received

daily Koate 3000 IU injection and treatment for his history of heart disease (Aspirin 1x80 mg; Clopidogrel 1x75 mg; Candesartan 1x16 mg; Diltiazem HCl 1x100 mg; Furosemide 40 mg 1-0-0). On the next day (4th November 2019), patient was given his first packed red cell (PRC) transfusion. However, on the next two days (5th and 6th November 2019), painful swelling appeared on patient's legs followed by nosebleed. Second PRC transfusion was given, and anticoagulant drugs were removed from the treatment plan. Nosebleed stopped immediately, after that, patient resumed his third and fourth bag of PRC transfusion. On 7th November 2019, mixing study was done. Patient's aPTT mixed with normal plasma before incubation is 41 seconds and after incubation became 59 seconds. aPTT is corrected with addition of normal plasma but became prolonged after incubation. From the mixing study, it can be concluded that patient has time dependent FVIII antibody and his diagnosis became Acquired Hemophilia A. Methylprednisolone 0.5 mg/kg/day was added to his treatment following his diagnosis.

On his sixth day of hospital stay (9th November 2019), the swollen joints lessened. Repeated blood test showed slight improvement in his hemoglobin after 4 bags of blood transfusion (6.2 mg/dL), aPTT drastically shortened after methylprednisolone consumption (27.2 seconds), and INR was still high (1.33). Tranexamic acid injection was stopped while other treatment continues. One bag of PRC transfusion was given on his eight day of hospital stay (11th November 2019). Patient's condition had significantly improved with no abnormalities observed on examination. Blood test on 15th November 2019 showed hemoglobin increased significantly to 10.5 mg/dL, aPTT had decreased (59 seconds), and INR also decreased (1.23). Patient then discharged with take-home medications such as methylprednisolone 16 mg (2-2-0), Aspirin 1x80 mg; Candesartan 1x16 mg; Diltiazem HCl 1x100 mg; and Furosemide 40 mg).

DISCUSSION

Acquired hemophilia A (AHA) is a disease caused by autoantibody which impairs factor VIII function in individual with no previous history of hemophilia. It is a rare condition generally occurs in older people (median age of diagnosis is between 60-67 years) and when the body's immune system attacks or disables a certain protein that helps the blood clot. Clinical manifestations associated with AHA are acute onset of severe and life-threatening bleeding or widespread subcutaneous bleeds; bleeding sites atypical of congenital hemophilia; high mortality with both early and late deaths; presence of underlying diseases and conditions; and advanced age. Other symptoms include ecchymosis; soft tissue hematoma; retroperitoneal hematoma; mucosal bleeding; prolonged postoperative bleeding; and hemarthrosis[7]. In this patient, the most prominent AHA characteristics are acute onset of bleeding; advanced age (60 years old); and hemarthrosis.

Most AHA cases are idiopathic (51.8%). The remaining cases are attributed by malignancy (11.8%), autoimmune disease (11.6%), pregnancy (8.4%), infection (3.8%), drug induced (3.4%), monoclonal gammopathy (2.6%), polymyalgia rheumatica (2.2%), dermatology disorders (1.4%), blood product transfusion (0.8%), and others (8.2%). Drug induced AHA can be caused by several medications, including antibiotics (penicillin, sulfonamides, chloramphenicol), anticonvulsants (phenytoin), methyldopa, interferon-α, clopidogrel, fludarabine[8]. In this case, patient has a history of PCI with routine consumption of clopidogrel and aspirin for 3 months. Past case reports have shown the increasing of aPTT after treatment using clopidogrel[9]. Clopidogrel therapy for 3 months

is suspected as a cause of AHA emergence in this patient.

AHA should be considered in patients, especially the elderly and peripartum and postpartum women, with recent onset of abnormal bleeding, and unexplained isolated prolongation in aPTT and normal PT. In non-bleeding patient not on anticoagulation, AHA should be suspected if there are isolated prolonged aPTT, a mixing study consistent with an inhibitor, and a negative lupus anticoagulant. Diagnosis should be confirmed by isolated prolongation of aPTT not corrected by mixing study. Once lupus anticoagulants and acquired von Willebrand syndrome have been excluded, AHA diagnosis can be confirmed by reduced FVIII levels and evidence of FVIII inhibitor[7]. Diagnosis algorithm for suspected AHA cases can be seen in figure 1. In this case, patient's aPTT mixed with normal plasma before incubation is 41 seconds and after incubation became 59 seconds. aPTT is corrected with addition of normal plasma but became prolonged after incubation. From this examination it can be concluded that patient has time dependent FVIII antibody.

Management strategy in AHA patients include two main objectives: short-term goal

Table 1. Bleeding medications for acquired hemophilia[10]

Medication	Dosage
Human FVIII concentrate	50-100 u/kg i.v. every 8-12 hours or in continuous intravenous infusion
Porcine FVIII concentrate	50-100 u/kg i.v. every 8-12 hours
Desmopressin	0.3-0.4 µ/kg (in 100 ml 0.9% NaCL) in intravenous infusion of a minimal duration of 30 minutes every 24 hours
aPCC	50-100 u/kg i.v. every 8-12 hours (maximun : 200U/Kg/day)
rVIIa	70-90 µg/kg i.v. every 2-3 hours
Tranaxemic acid	15 mg/kg p.o. or i.v. every 8 hours (daily dose is usually 3 x 1.0 g)

Table 2. Immunosuppressive drugs commonly used to eradicate FVIII antibodies[10]

Medication	Dosage
Prednisone	1 mg/kg/day p.o. for max. 4-6 weeks
Cyclophosphamide	1,5-2mg/kg/day p.o. for max 4-6 weeks
Azathioprine	2 mg/kg/day p.o. (maximum dose/day 150 mg)
Cyclosporine	5mg/kg/day po for 6 days. Continue 2,5 - 3 mg/kg/day
IVIg	0.3-0.4 g/kg/day for 5 days or 1g/kg/day for 2 days
Rituximab	375 mg/m^2 once a week for ≥ 4 consecutive weeks
Vincristine	1 mg/m^2 i.v. (max. single dose 2 mg)
2-chlorodeoxyadenosine	0.1 mg/kg in a 24-h i.v. infusion for 7 days or 0.14 mg/kg body weight in a 2-h i.v. infusion for 5 days
Micofenolat mofetil	1 gr/day po for 7 days, and increase until 2g/day

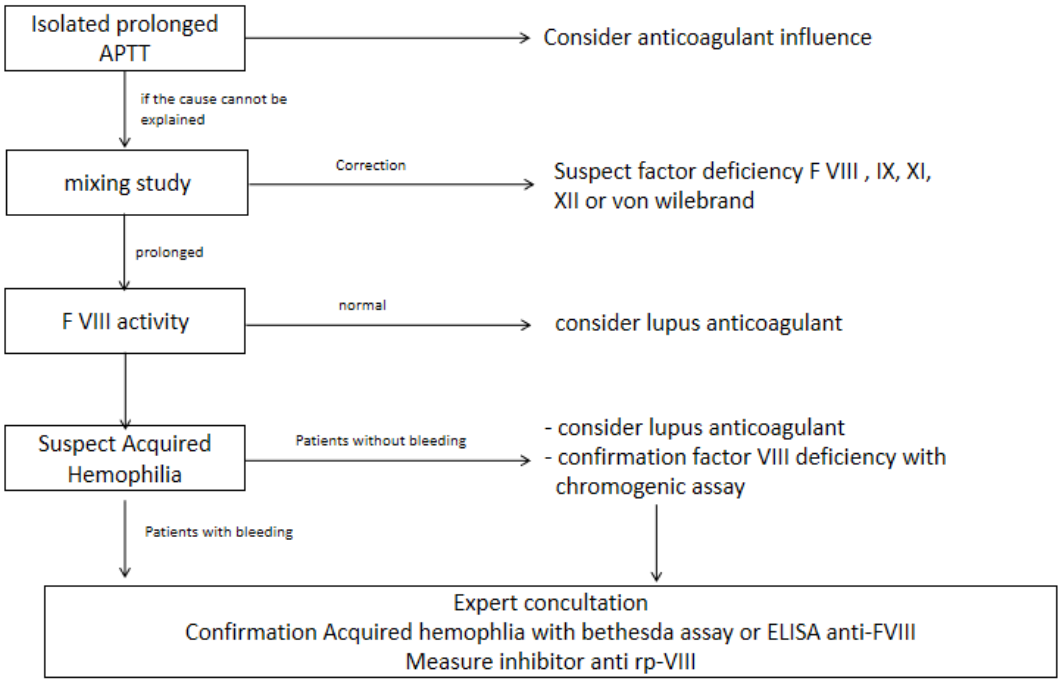

Figure 1. Diagnosis algorithm with suspected acquired hemophilia[1]

of bleeding treatment and prophylaxis, and long-term goal of inhibitor elimination[8]. Available hemostatic therapy used among others, recombinant porcine FVIII (rpFVIII), activated prothrombin complex concentrate (aPCC), recombinant activated FVII (rFVIIa), human FVIII (hFVIII), desmopressin, and antifibrinolytics. Human FVIII and rpFVIII act as replacement therapy, whereas aPCC and rFVIIa as a bypass therapy[11]. Bleeding treatment depends on the antibody titer. However, on this patient, quantitative inhibitor screening has not been done. Patient with high-titer antibody (>5 BU/mL) should be given aPCC or rFVIIa, while patient with low-titer antibody (<5 BU/mL) should be given human factor VIII concentrate, very rarely desmopressin. Both rFVIIa and aPCC are safe for management of bleeding in acquired hemophilia, but rFVIIa does not cause anamnestic response of anti-FVIII as observed sometimes after aPCC[12]. Eliminating inhibitors is done through the work of immunosuppressant agents. The first-line treatment for eradicating inhibitors are corticosteroids, or corticosteroids + cyclophosphamide[13].

The second-line treatment is rituximab, while the alternative treatments are azathioprine, vincristine, mycophenolate, cyclosporine[13]. This patient is given methylprednisolone 0.5 mg/kg/day continued to 1 mg/kg/day, as per recommendation. The dosage for AHA medications can be seen in table 1 and 2. Short-term, high-dose immunosuppressive treatment with oral prednisone (1 mg/kg for 10 days, 0.5 mg/kg for 20 days, and 0.25 mg/kg for 15 days) can reduce the incidence of angiographic restenosis with minor secondary effects such as gastric pain, water and salt retention, and worsened hypertension in nearly 10% patients[14]. Prolonged corticosteroid use can elevate various lipid subfractions mediated by increased plasma insulin levels, impaired lipid catabolism, and increased lipid production in the liver – which leads to higher coronary artery disease risk[15].

The limitation of this case report was not definitely examine FVIII to diagnose

Hemophilia A due to lack of the laboratory accessibility.

CONCLUSIONS

Diagnosis of acquired hemophilia A should be considered in patients of old age with prolonged aPTT while having no previous history of spontaneous bleeding. Many factors that can trigger AHA should be considered such as pregnancy, autoimmune disease, infection, drug usage, even though most AHA cases are idiopathic. Probable cause of AHA in this patient is clopidogrel usage for 3 months after PCI. After assessing patient's clinical status, laboratory test of aPTT correction test should be done to establish diagnosis of AHA. This patient had prolonged aPTT after correction, which leads to the diagnosis of AHA. Discharge treatment for this patient was methylprednisolone 0.5 mg/kg/day continued to 1 mg/kg/day. Corticosteroid therapy must be adjusted while considering patient's comorbid factor of CAD 3 VD. Quantitative inhibitor screening should be done next to determine bleeding risk and choose the best bleeding therapy for this patient

REFERENCES

1. Yousphi, A. S. et al. Acquired Hemophilia A: A Rare but Potentially Fatal Bleeding Disorder. Cureus 2019;11(8).
2. Leissinger, C. A., Kruse-Jarres, R. and Janbain, M. Acquired hemophilia A: emerging treatment options. Journal of Blood Medicine 2015;201:143
3. Collins P, Baudo F, Huth-Kühne A, IngerslevJ, Kessler CM, Castellano MEM, et al.Consensus recommendations for the diagnosis and treatment of acquired hemophilia A. BMC Research Notes. 2010;3(161).
4. Baudo F, Collins P, Huth-Kuhne A, Le´vesque H, Marco P, Nemes L, et al. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. Blood. 2012;120(1):39-46
5. Collins PW. Management of acquired haemophilia A. Journal of Thrombosis and Haemostasis. 2011;9(Suppl 1):226-35.
6. Janbain M, Leissinger CA, Kruse-Jarres R. Acquired hemophilia A: emerging treatment options. Journal of Blood Medicine. 2015;6:143-50.
7. Kessler, C. M. and Knöbl, P. Acquired haemophilia: An overview for clinical practice. European Journal of Haematology 2015; 95:36–44.
8. Kruse-Jarres, R. et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. American Journal of Hematology 2017;92(7);695–705.
9. Hwang, H. W. *et al.* A patient with acquired hemophilia A induced by clopidogrel. Korean Journal of Hematology 2012; 47(1):80–82.
10. Purwanto, Ibnu. Tinjauan terkini hemofilia A yang di dapat : aspek diagnosis dan manajemen. Smart Medical Journal 2020; 3 (2) : 79 – 89
11. Windyga J, Baran B, Odnoczko E, Buczma A, Drews K, Laudanski P, et al. Treatment guidelines for acquired hemophilia A. Ginekologia Polska. 2019;90(6):353-64.
12. Tiede A, Collins P, Knoebl P, Teitel J, Kessler C, Shima M, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020;105(7):1791-801.
13. Windyga, J. et al. Treatment guidelines for acquired hemophilia A. Ginekologia Polska 2019;90(6):353–364.
14. Ferrero V, Ribichini F, Pesarini G, Brunelleschi S, Vassanelli C. Glucocorticoids in the prevention of restenosis after coronary angioplasty: therapeutic potential. Drugs. 2007;67: 1243–1255.
15. Sholter D, Armstrong P. Adverse effects of corticosteroids on the cardiovascular system. Can J Cardiol. 2000;16(4):505-511