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A Chronic Hemophilia Patient With Manifestations of Spontaneous Penile Bleeding and Multiarthropathy

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Abstract: Hemophilia A is a hereditary bleeding disorder characterized by Factor VIII deficiency, with varying severity levels. This report presents a 27-year-old male patient with moderate Hemophilia A who experienced spontaneous penile bleeding and a history of multiarthropathy. The patient reported recurrent bleeding episodes since childhood and received Factor VIII therapy, resulting in significant symptom relief. This case highlights the importance of individualized management in chronic hemophilia, focusing on preventive measures to mitigate future bleeding episodes and comorbidities, thereby improving quality of life and life expectancy. **Case report :** A 27-year-old male patient presented with spontaneous penile bleeding triggered by minor trauma and associated with moderate Factor VIII deficiency (1%). Past medical history included recurrent joint and gastrointestinal bleeding episodes. The patient responded positively to Factor VIII therapy and packed red cell transfusions, with symptom resolution after 10 days of hospitalization. Family pedigree analysis and coagulation studies confirmed the diagnosis of moderate Hemophilia A. **Discussion :** Hemophilia A patients face lifelong bleeding risks, with multiarthropathy as a common complication. Factor VIII levels closely correlate with disease severity and bleeding manifestations. Preventive therapy, including Factor VIII administration, is crucial for minimizing complications. Additionally, managing viral infection risks is essential due to associated sexual behavior in certain demographics. Regular screening and patient education play pivotal roles in comprehensive care. **Conclusion :** This case underscores the significance of proactive management in moderate Hemophilia A, emphasizing tailored therapy and preventive strategies. Ensuring adequate access to clotting factor concentrates and addressing comorbidities can significantly enhance the quality of life and prognosis for chronic hemophilia patients.

Keywords: Hemophilia A, Factor VIII Deficiency, Bleeding Disorder, Multiarthropathy, Penile Bleeding

INTRODUCTION

Over the past decades, life expectancy for patients with Hemophilia A and Hemophilia B has increased, primarily due to advancements in healthcare centers, the availability of coagulation factor concentrates, and treatments for infectious diseases (1). The improvement in life expectancy and quality of life has led to a growing population of hemophilia patients in the adult and elderly age groups, who also face health conditions commonly associated with aging (2). Before the availability of factor concentrate therapy, most hemophilia patients succumbed

to bleeding complications (3). During the 1980s and 1990s, the highest mortality rates were attributed to viral infections, although bleeding episodes remained a leading cause of death.

The average life expectancy for male hemophilia patients in the early 20th century was 11 years, which then increased to a survival range of 55 to 63 years by the 1970s (4). In the 1980s, survival rates further improved, reaching up to 68 years in Europe (5). However, during the 1990s, life expectancy declined to just 49 years due to various viral infections. With advancements in viral infection management, studies showed that life expectancy for male hemophilia patients increased again by 2007, with a study in Italy reporting a peak survival age of 60 years (6). This highlights the achievement of life expectancy for hemophilia patients approaching that of the general population, although the distribution remains predominantly among young adult hemophilia patients rather than the elderly (4).

Chronic hemophilia patients, predominantly consisting of young adults, require significant attention, particularly regarding the various comorbidities that may accompany the progression of chronic hemophilia. Alongside efforts to prevent bleeding episodes, a comprehensive study of these comorbidities is essential. This paper presents a case report of a chronic hemophilia patient with multiarthropathy and other associated comorbidities. It is hoped that this discussion will expand our understanding of managing chronic hemophilia, focusing not only on treating bleeding episodes but also on preventing complications to reduce future bleeding risks and improve the life expectancy of these patients.

METHOD

A 27-year-old male patient, Mr. S, of Javanese ethnicity, a Muslim, and working as a private employee at a salon, residing in Sesetan, Denpasar, Bali, presented with complaints of bleeding at the tip of his penis, which he had been experiencing since one day before admission. The patient reported that the bleeding started due to a scratch caused by a zipper accident a day prior. The bleeding continued to seep and drip, occasionally accompanied by mild pain during urination. At home, the patient attempted to bandage the bleeding area, but the blood continued to seep. He sought treatment at a general clinic where he was prescribed oral tranexamic acid 500 mg three times a day. Subsequently, he was referred to Sanglah General Hospital.

The patient has experienced multiple episodes of bleeding in the past, with the most recent hospitalization occurring at the age of 13 at Soetomo General Hospital due to rectal bleeding, which was attributed to hard stools. He was diagnosed with Hemophilia A after undergoing a Factor VIII test. During that time, he was hospitalized several times for bleeding and joint pain, with improvement following the administration of Factor VIII. Regarding family history, the patient is the first member of the family to present with such complaints. A pedigree analysis revealed that he is the second child of two siblings, with the first child, a male, reported to be healthy. Both the patient's father and mother are currently healthy and have never experienced similar complaints.

Physical examination revealed the patient was fully conscious (E4; V5; M6) with a generally weak condition. His weight was 40 kg, height 156 cm, blood pressure 120/80 mmHg, pulse 88 beats per minute, respiratory rate 20 breaths per minute, and axillary temperature 36.8ºC. Examination of the head and neck showed no signs of anemia, jaundice, cyanosis, shortness of breath, or lymph node enlargement. Chest examination revealed normal heart sounds (S1 and S2) with no additional sounds. Lung examination showed vesicular breath sounds with no rales or wheezing. Abdominal examination revealed no palpable liver or spleen, no distension, and normal bowel sounds. Examination of the extremities showed no edema in both legs, and the extremities were warm to the touch.

Laboratory results showed a leukocyte count of 7.31 K/uL (normal: 4.5-11 K/uL), hemoglobin 8.42 g/dL (normal: 13.5-18.0 g/dL), hematocrit 25.4% (normal: 40-54%), MCV 79.5 fl (normal: 80-94 fl), MCH 26.4 pg (normal: 27-32 pg), and platelets 385 K/uL (normal: 150-440 K/uL). Coagulation tests revealed a bleeding time (Duke) of 2.0 minutes (normal: 1-3 minutes), clotting time (Lee & White) of 14.0 minutes (normal: 5-15 minutes), prothrombin

time (PT) of 21 seconds (normal: 12-18 seconds), and activated partial thromboplastin time (APTT) of 96 seconds (normal: 22.6-35 seconds). Liver function tests showed AST 27 mg/dL (normal: 14-50 mg/dL), ALT 33 mg/dL (normal: 11-64 mg/dL), total bilirubin 0.6 mg/dL (normal: 0.0-1.0 mg/dL), direct bilirubin 0.1 mg/dL (normal: 0.0-0.3 mg/dL), cholesterol 26 mg/dL (normal: 110-200 mg/dL), and albumin 3.8 g/dL (normal: 4.0-5.7 g/dL). Factor VIII activity was found to be 1%, while inhibitor testing could not be performed due to facility limitations. HIV, HBsAg, and anti-HCV tests were non-reactive.

Based on the data, the patient was diagnosed with Hemophilia A accompanied by penile bleeding. From the first to the third day of hospitalization, the patient received 10 vials of fresh frozen plasma (FFP) daily, but the bleeding persisted. On the third day, cryoprecipitate was administered, which led to a relative reduction in bleeding; however, the bleeding recurred on the fourth day. On the fifth day, the patient received Factor VIII (Koate), and APTT improved, returning to the normal range after the first administration of 1500 IU of Factor VIII. The patient was then given 1500 IU of Factor VIII every 12 hours along with PRC transfusions. The penile bleeding ceased on the eighth day of treatment. On the ninth and tenth days, the patient was free of penile bleeding, and the administration of Factor VIII was discontinued. However, on the eleventh day, the patient reported difficulty defecating and excessive straining due to hard stools, which resulted in hematochezia. Factor VIII was re-administered at 1500 IU every 12 hours along with PRC transfusions, and the bleeding stopped on the fifteenth day of treatment.

RESULT AND DISCUSSION

Hemophilia A is the most common type of hemophilia. Due to its X-linked recessive inheritance pattern, males are typically affected and present with clinical manifestations of bleeding, while females are usually carriers of the trait.The diagnosis of Hemophilia A is established based on the following criteria: (i) the presence of family members with a history of abnormal bleeding, (ii) an X-linked recessive inheritance pattern, (iii) prolonged activated partial thromboplastin time (APTT) observed in coagulation tests, and (iv) reduced levels of Factor VIII (7).

the aforementioned case, three out of the four diagnostic criteria for Hemophilia A were met: (i) a history of abnormal bleeding, including frequent bleeding episodes since the age of 13, severe bleeding, and melena, and (iii) a prolonged APTT of 96 seconds. Additionally, (iv) the Factor VIII level was 1%, indicating moderate deficiency.

The closest differential diagnoses for Hemophilia A are Hemophilia B and Von Willebrand Disease (VWD). All three conditions are hereditary bleeding disorders; however, they differ in their inheritance patterns. Hemophilia A and B are X-linked, while VWD follows an autosomal recessive inheritance pattern.

Hemophilia A must also be differentiated from Von Willebrand Disease (VWD). In VWD, the inheritance pattern is autosomal recessive, meaning that if it appears in more than one family member, it typically affects siblings (brothers or sisters) of the patient rather than parents, children, or other relatives. The risk of phenotypic manifestation in siblings is 1:4, and it can occur in both sexes. Another distinguishing feature of VWD is a prolonged bleeding time and reduced von Willebrand factor levels.

The clinical manifestations of Hemophilia A can affect various systems of the body, primarily the musculoskeletal system, central nervous system, gastrointestinal tract, and urinary tract. Bleeding may occur spontaneously or post-trauma, manifesting in both young and adult patients. Joint involvement (hemarthrosis), characterized by recurrent joint pain accompanied by hematomas, is a dominant feature in the clinical course, often leading to deformities and limping. Severe bleeding can occur following medical procedures such as tooth extractions, surgeries, or trauma. Hematuria is more common than gastrointestinal bleeding, such as hematemesis, melena, or rectal bleeding. Although rare, spontaneous intracerebral hemorrhage can occur and is a significant cause of mortality in patients with severe clinical manifestations.

The severity of bleeding manifestations depends on the plasma activity level of Factor VIII, as shown in the accompanying table (8).

Tabel : 1. Klasifikasi klinis Hemofilia A [8]

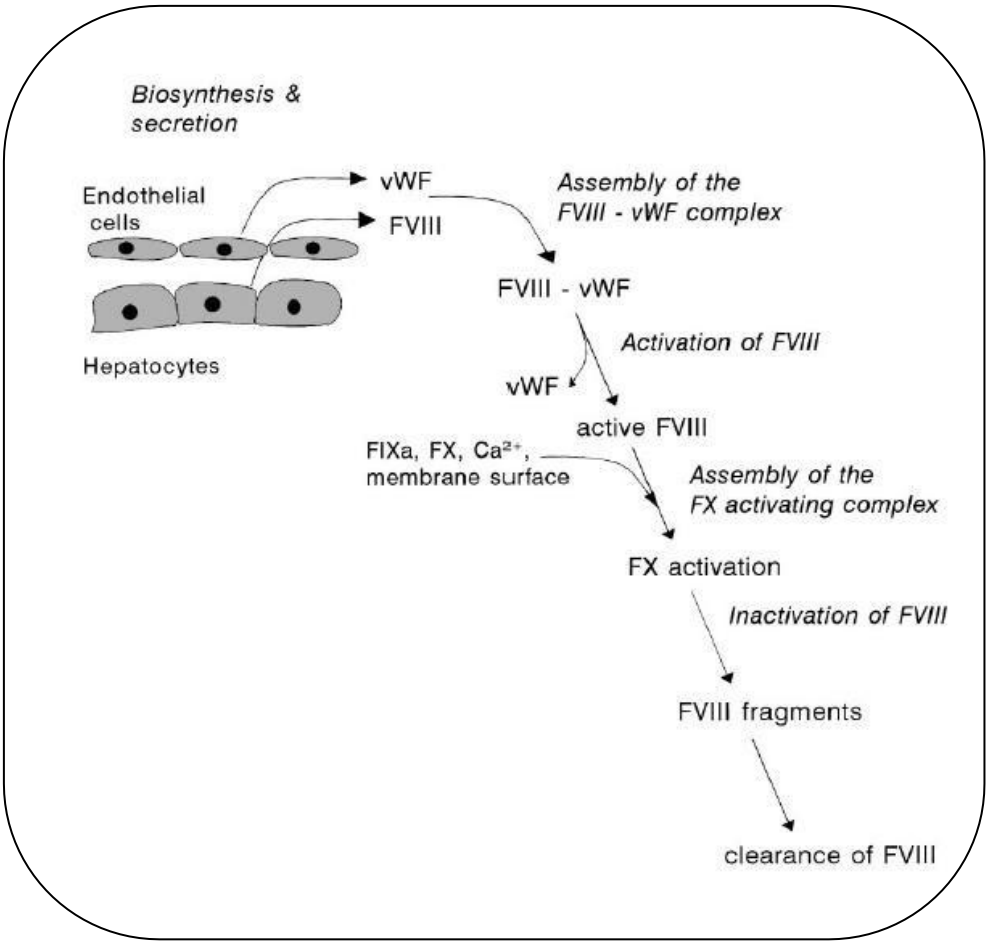
Klasifikasi	Kadar faktor VIII	Gambaran Klinis
Severe	< 1 % (< 0,01 U/ml)	Hemarthrosis & perdarahan spontan sering dan berat sejak muda, umumnya disertai deformitas sendi dan kecacatan.
Moderate	1-5 % (0,01 – 0,05 U/ml)	Perdarahan spontan jarang, perdarahan berat setelah luka kecil.
Mild	5-25 % (0,05 – 0,25 U/ml)	Perdarahan spontan jarang, perdarahan setelah trauma atau setelah operasi.

In this case, the patient presented with penile bleeding, accompanied by a history of childhood bleeding episodes and severe bleeding following tooth extraction and hematochezia. Based on the clinical symptoms, the bleeding in this case is classified as moderate, with a Factor VIII level of 1%. Although the bleeding began at a young age, it was typically triggered by factors such as trauma or prolonged use of joint-related medications. The bleeding improved with Factor VIII therapy, allowing the patient to survive until the age of 27. Penile bleeding is a very rare clinical presentation. Initially, it was attributed to trauma caused by a zipper injury; however, further history-taking revealed that the patient admitted the bleeding occurred following same-sex sexual activity. The patient is a man who has sex with men (MSM) and disclosed having a same-sex partner for the past six months. This places the patient in a high-risk category for viral infections such as HIV, hepatitis B, and hepatitis C. However, in this case, screening results for all viral markers were non-reactive.

Factor VIII is a single-chain coagulation protein that regulates the activation of Factor X via proteases produced by the intrinsic coagulation pathway. This protein is synthesized in liver parenchymal cells and circulates in complex with von Willebrand factor. Normal hemostasis requires a minimum Factor VIII activity of 25%. Hemophilia symptoms occur when functional circulating Factor VIII levels are less than 5%, with Factor VIII levels closely correlating with the clinical severity of the condition. Its half-life, as reported in studies, varies but is predominantly in the range of 11–14 hours.

To function as an effective cofactor for the activation of Factor IXa, Factor VIII must first be activated by thrombin, forming a heterotrimer composed of the A1, A2, and A3-C1-C2 domains. Activated Factor VIII (Factor VIIIa) and Factor IXa, which bind to the platelet surface, form a functional complex that activates Factor X. The presence of active Factor VIII significantly accelerates the activation of Factor X by active Factor IX. This explains the similar clinical manifestations in Hemophilia A and B, as both Factor VIII and Factor IX are essential for the formation of the Xase complex.

The mechanism of normal hemostasis in the activation of the intrinsic pathway begins with the contact between Factor XII and Factor XI with a foreign surface outside the lumen of normal blood vessels. This interaction leads to the activation of Factor XI, initiating a cascade that ultimately contributes to blood clot formation.



The characteristics of adult hemophilia patients have begun to attract attention as the life expectancy of individuals with hemophilia has increased, with many now approaching the normal life expectancy of the general population (9). In developed countries, hemophilia is commonly observed in adult and elderly age groups. However, further research is still needed to investigate the various comorbidities beyond bleeding episodes that may contribute to mortality among adult and elderly hemophilia patients.

Male hemophilia patients face similar health risks to the general male population as they age, particularly in developed countries where adequate clotting factors are available (10). The processes of growth and aging not only result in complications directly related to hemophilia, such as arthropathy and viral infections, but also contribute to the development of other conditions, including cardiovascular disease, malignancies, osteoporosis, and more. Currently, there are limited guidelines for managing comorbidities in adult and elderly hemophilia patients and understanding how these conditions impact the underlying disease. In this case, the patient belongs to the productive age group, with young adults still dominating the demographic distribution of chronic hemophilia cases. Studies and evaluations focusing on various comorbidities are essential to extend the survival of these patients.

Joint arthropathy is the most common complication in patients with Hemophilia A and B, characterized by frequent spontaneous bleeding in the joints and muscles, leading to the development of arthropathy over the course of the disease. Several studies have demonstrated that prophylactic inhibitor therapy can reduce the risk of developing arthropathy (11, 12). Other research has shown that prophylactic administration of clotting factors reduces the incidence of arthropathy compared to on-demand therapy in pediatric populations. Additionally, studies indicate that hemophilia patients, particularly those over 65 years of age who had limited access

to factor concentrates during adolescence, are prone to developing hemophilic arthropathy. This condition is marked by typical joint deformities, muscle weakness, and proprioceptive impairments, all of which significantly impact quality of life.

Studies indicate that arthropathy in both middle-aged and elderly hemophilia patients involves multiarthropathy in approximately 57% of cases, affecting six or more joints (13, 14). Adult hemophilia patients also report higher pain intensity scores compared to the general population. Additionally, literature highlights that arthroplasty is performed in about 46% of hemophilia patients in developed countries, compared to only 7% in non-hemophilia populations (14). Common surgical procedures include ankle arthrodesis, osteotomy, and hip or knee arthroplasty. The primary indications for joint surgery in hemophilia patients are chronic and persistent joint pain, disability, and failure of conservative therapies to improve joint function. In chronic hemophilia patients, particularly elderly individuals, decreased proprioception significantly increases the risk of falls, occurring in approximately 70% of elderly hemophilia patients and 25% of adult hemophilia patients. These falls may occur spontaneously or when encountering obstacles during walking or mobilization (14).

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Chronic viral infections such as HIV, Hepatitis B, and Hepatitis C remain prevalent among the adult hemophilia subgroup in studies from previous decades (17). It is crucial to assess the risk of hepatocellular carcinoma (HCC) in chronic adult hemophilia patients co-infected with Hepatitis C, particularly those with genotype 1 and/or HIV co-infection, especially if they fail to achieve a sustained virological response through Pegylated Interferon and Ribavirin therapy. Periodic ultrasound screening is recommended for adult hemophilia patients with any of these viral comorbidities to enable early detection of cirrhosis and/or HCC, which may predispose patients to gastrointestinal bleeding (3).

For adult hemophilia patients co-infected with HIV, some literature reports improved survival rates in those receiving highly active antiretroviral therapy (HAART) and adhering to regular treatment regimens (18, 19). The patient in this case works at a salon and is at risk due to homosexual behavior, with a secondary job as a bar employee. Viral marker screening remains essential given the patient's high-risk status. Supporting laboratory investigations showed non-reactive results for HIV, Hepatitis B, and Hepatitis C. Patient education on avoiding multiple partners and practicing safe sexual behaviors, including condom use, is strongly recommended to prevent viral infections.he development of inhibitors remains a significant challenge in the management of hemophilia.

A study involving data from large healthcare centers in the United States and Europe estimated a cumulative risk of inhibitor formation in adult hemophilia A patients at 30% by the age of 50 and 36% by the age of 75 (20). Moderate hemophilia patients are at increased risk of developing inhibitors later in life, particularly following intensive exposure to Factor VIII concentrates due to massive bleeding episodes, preoperative preparation, or postoperative management after invasive procedures. Literature suggests that inhibitor formation is associated with specific genetic mutations, such as Arg531Cys, and intensive exposure to clotting factor concentrates (21).

The management of acute bleeding in adult hemophilia patients with inhibitors involves the use of activated prothrombin complex concentrate (APCC) and recombinant Factor VIIa (rFVIIa), with rapid bleeding control being the key to achieving optimal therapy. This approach helps reduce complications, particularly in preserving joint and musculoskeletal function in hemophilia patients with inhibitors (22).

There is limited literature on the safety of rFVIIa administration in elderly and adult hemophilia patients. One article describes the use of Immune Tolerance Induction (ITI) in a 60-year-old hemophilia patient (23). Another study highlights Rituximab as an effective immune tolerance agent for eradicating inhibitors in adult and elderly hemophilia patients (10). In this case, careful consideration is required when administering Factor VIII concentrates. While prophylactic administration can reduce complications such as polyarthropathy, it may also trigger inhibitor formation. Therefore, on-demand treatment is prioritized in this case to balance efficacy and risk.

Malignancy is another aspect that needs attention, as adult and elderly hemophilia patients are at a similar risk of developing malignancies as the general population as they age. However, literature on malignancies in hemophilia often emphasizes hepatocellular carcinoma (HCC) due to the high prevalence of Hepatitis C infections in hemophilia patients (4). Some studies indicate that severe hemophilia does not increase the incidence of other malignancies compared to the general population. In fact, these studies suggest that hemophilia may reduce the risk of malignancy (20).

In vitro research shows that congenital prothrombin disorders can inhibit or reduce metastasis. Experiments in hemophilic mice demonstrated a lower incidence of metastases compared to non-hemophilic mice in a melanoma model. This may be explained by reduced thrombin formation, which is associated with decreased metastasis (24). Thus, congenital bleeding disorders may have a protective effect against malignancies, particularly metastatic progression.

Beyond HCC, other malignancies that may affect adult and elderly hemophilia patients include prostate, skin, and gastrointestinal cancers, with incidence rates comparable to the general population (10). It is important to note that congenital bleeding disorders increase the risk of hemorrhage during chemotherapy and radiation therapy, which are often part of malignancy treatment. The administration of clotting factor concentrates is essential as both a therapeutic and prophylactic measure, especially during surgical interventions for malignancy (25).

Malignancies such as prostate and colon cancer, which are prevalent in this population, further heighten the risk of bleeding. Currently, there are no clear recommendations for managing clotting factor concentrate therapy in hemophilia patients with malignancies, whether in adulthood or old age.

In this case, the patient falls into the category of chronic hemophilia within the productive age group. While most literature emphasizes malignancy screening in elderly patients, preventive measures should be a focus at this stage of life. For instance, HCC prevention can be achieved by mitigating Hepatitis B and C infections through vaccination and early detection.

Chronic pain is a significant issue among adult and elderly hemophilia patients, as effective pain control can greatly improve their quality of life, especially when the pain is due to joint deformities. First-line management of chronic pain typically involves the use of paracetamol and NSAIDs. However, prolonged use of these medications increases the risk of NSAID-induced gastropathy and gastrointestinal bleeding in this group (26). Additionally, in hemophilia patients with viral infections, prolonged NSAID use may worsen liver function.

COX-2 inhibitors are recommended as an alternative to NSAIDs for better gastrointestinal safety. If chronic pain remains uncontrolled, the use of codeine or other narcotic preparations may be considered, tailored to the intensity of the pain scale (25). Preventive efforts, such as physiotherapy and hydrotherapy, are strongly recommended to maintain joint functionality and reduce the incidence of chronic pain in adult and elderly hemophilia patients.

In this case, the patient uses paracetamol for pain relief on an as-needed basis. Long-term use of pain medications is not advised to prevent NSAID-induced gastropathy and the associated risk of upper gastrointestinal bleeding. Physiotherapy and light joint exercises, such as walking, are recommended to preserve joint functionality and alleviate chronic pain.

CONCLUSION

A case has been reported of a 23-year-old male of Javanese ethnicity presenting with penile bleeding and a history of hemophilia. The diagnosis was established through a thorough history-taking process, including exploring the patient's family pedigree and a history of prolonged bleeding episodes since childhood. This was supported by physical examination and basic laboratory tests, which revealed a prolonged APTT and a Factor VIII level of 1%. Based on the X-linked recessive inheritance pattern and the moderate severity of the bleeding, the patient was classified as having moderate Hemophilia A. The patient responded well to Factor VIII administration and packed red cell transfusions. The chronic nature of hemophilia in this patient highlights the importance of preventive measures to reduce the risk of future bleeding episodes, thereby improving the life expectancy of chronic hemophilia patients.

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