Acquired Immunodeficiency Syndrome in Hemophilia A: A Case Report and Literature Review

Vy Dang Karp, PharmD, BCSCP
Optum Infusion Services

Eunjung Kim, PharmD, BCSCP
Optum Infusion Services

Lisa Schrade, PharmD
Optum Infusion Services

Nidhi Thaker-Mehta, PharmD
Optum Infusion Services

ABSTRACT

Background

Hemophilia is an X-linked recessive coagulation disorder which is characterized by factor VIII deficiency. Hemophilia A is the most common inherited bleeding disorder, accounting for up to 85% of the hemophilia population worldwide. The association between hemophilia A and acquired HIV/AIDS is infrequently seen in practice nowadays. We present a rare case of congenital hemophilia A with acquired HIV/AIDS due to contaminated plasma products during the HIV epidemic between the 1980s and 1990s.

Case Presentation

We report a case of a 50-year-old male with a complicated medical history of moderate to severe congenital hemophilia A, immune thrombocytopenia, multiple episodes of upper gastrointestinal (GI) bleeding, target joint bleeding, arthritis, and acquired HIV/AIDS. The prolonged partial thromboplastin time (PTT) of 32.5 secs and baseline FVIII of 0-3% confirmed the diagnosis of hemophilia A. Medical records revealed the patient was treated with cryoprecipitate and factor concentrates for hemophilia in early childhood. Aggressive HIV/AIDS regimens were given along with long-term antibiotics for opportunistic infections. A literature review was performed to identify similar unique cases of this rare association.

Conclusion

Acquired HIV/AIDS present in hemophilia A patients is not commonly seen in practice. The plasma contamination tragedy enforced stringent regulations and guidelines on the manufacturing industry. Remarkably, hemophilia patients can now achieve a longer lifespan and quality of life through novel hemophilia treatment.

Keywords: Hemophilia A, AIDS/HIV, Factor VIII activity, Contaminated plasma products.

Introduction

Hemophilia A is an X-linked recessive coagulation disorder characterized by factor VIII deficiency. Hemophilia A is the most common bleeding disorder, accounting for 80-85% of the hemophilia population, with an occurrence rate of ~1 in 10,000 live births.[1] Carrier mothers often have a 50% chance of passing the mutated F8 gene to the male child. The spontaneous mutation of the F8 gene leads to abnormal production of factor VIII, which disrupts downstream regulation of the clotting cascade.

Hemostasis is important to maintaining hemodynamic stability and circulation. The 2 components of hemostasis are primary and secondary hemostasis. Primary hemostasis consists of platelet aggregation and platelet plug formation at the injury site. During an injury, platelets are exposed to the subendothelial space, where they aggregate and adhere to stop the bleeding. Fibrin can also activate platelets. Secondary hemostasis consists of the clotting cascade, which stabilizes the platelet plug and further repairs the site. The clotting cascade has 3 main pathways: extrinsic, intrinsic, and common pathway. The common pathway can be achieved by both the extrinsic and intrinsic pathways via activation of factor X to Xa. The final step of the clotting cascade occurs when fibrin and factor VIIIa stabilize the clot at the injury site by forming a cross-linked fibrin mesh.

Genomic studies suggest that mutations in F8 genes result in hemophilia A. F8 gene is a large structural complex with 26 exons, and it is located at the end of gene Xq28.[2] Various mutations of this gene, including inversion, insertion, missense, and deletion, cause hemophilia, but 50% of the cases are attributed to inversion mutations.[3] Factor activity (FA) level is used to classify patients into 3 severity scales: mild >5- 40%, moderate 1-5%, and severe <1%. Target joint hemorrhage is the most common complication in hemophilia A, often recurrent and localized to 1 joint. A meta-analysis study by Soucie et al. with 7,914 hemophilia patients noted that hemophilia A patients have a 30% higher risk of undergoing invasive orthopedic procedures than those with hemophilia B (p = 0.4). The study further demonstrated that an FA level of approximately 20% is required to prevent target joint hemorrhages, and the risk of orthopedic procedures is reduced by 40% for every 10% increase in FA.[4] This data shows the vast difference in clinical severity between hemophilia A and B.

For decades, clotting factors remained the therapy of choice, given their known safety and efficacy. Currently marketed products are either derived from human plasma donors or created by using DNA recombinant technology.

Case Report

A 50-year-old male with moderate to severe congenital hemophilia A presented to the hemophilia treatment center with chief complaints of bilateral knee and right shoulder pain. The patient denied gastrointestinal (GI) bleeding, fever, night sweats, weight loss, chest pain, and dyspnea. The patient had a baseline factor VIII level of 0-3% and an inhibitor titer of 0 Bethesda units (BU). His right knee was a target joint with additional hemophilic arthropathy issues in his right wrist and right shoulder. Complicated medical history included HIV, hepatitis C, immune thrombocytopenia (s/p splenectomy in 1/1985), *mycobacterium avium intracellular infection* (MAI), upper GI bleeding, arthritis secondary to hemophilic arthropathy, and chronic back pain due to a fall.

During his infancy, the patient had a prolonged bleeding post-circumcision. The extensive bruising was noted at his 6-month-old checkup, which led to further testing and diagnosis of hemophilia A. His bleeding disorder was initially treated with cryoprecipitate until he was 8 years old. Afterward, the treatment was replaced by on-demand FVIII replacement regimen, which consisted of 3,000 units for mild bleeding and 7,000 units for severe bleeding. In 2013, the patient was switched to prophylaxis therapy due to recurrent hospitalizations from gastrointestinal (GI) bleeding. The admission laboratory tests revealed a significantly low level of factor VIII activity, 22.4%, unremarkable inhibitor assay of 0 titers, and PTT of 32.5 seconds (H). His bleeding history prior to starting prophylaxis FVIII therapy included right iliopsoas hematomas, right elbow and right knee hemarthrosis, GI bleeding, right wrist hemophilic arthropathy/hemarthrosis, right shoulder pain with bicipital tendinopathy, and right hip pain related to iliopsoas bleeding. Upon multiple hospitalizations due to unrevoked GI bleeding, the patient was placed on an escalated prophylaxis dosing of FVIII replacement therapy with Kogenate 3,100 units 3 times weekly.

Status post splenectomy due to chronic ITP in 1984, he was diagnosed with acquired HIV and hepatitis C. The patient was treated with Zidovudine (Retrovir)

for 9 years, then therapy was discontinued, assumingly due to noncompliance. Ten years later, the patient was re-hospitalized due to MAI in the form of a neck mass; he was treated with clarithromycin, ethambutol, and rifabutin. Other readmission complications included candidal esophagitis and AIDS status. Diagnostic laboratory tests showed a critically low CD4/CD8 lymph ratio of 0.65 (L) and a CD4 count of 612/µL. HIV/AIDS treatment was reinitiated with Atripla (efavirenz, emtricitabine, tenofovir) and later changed to Odefsey (emtricitabine, rilpivirine, tenofovir) (serum creatinine 0.84mg/dL, eGFR >60 mL/min/1.73m2, ALT/AST 15 and 23U/L, respectively). His HIV viral load of 3970/mL had been intermittently detectable since 2012, while his hepatitis C viral load had been undetectable since his hospitalization in 2013.

Discussion

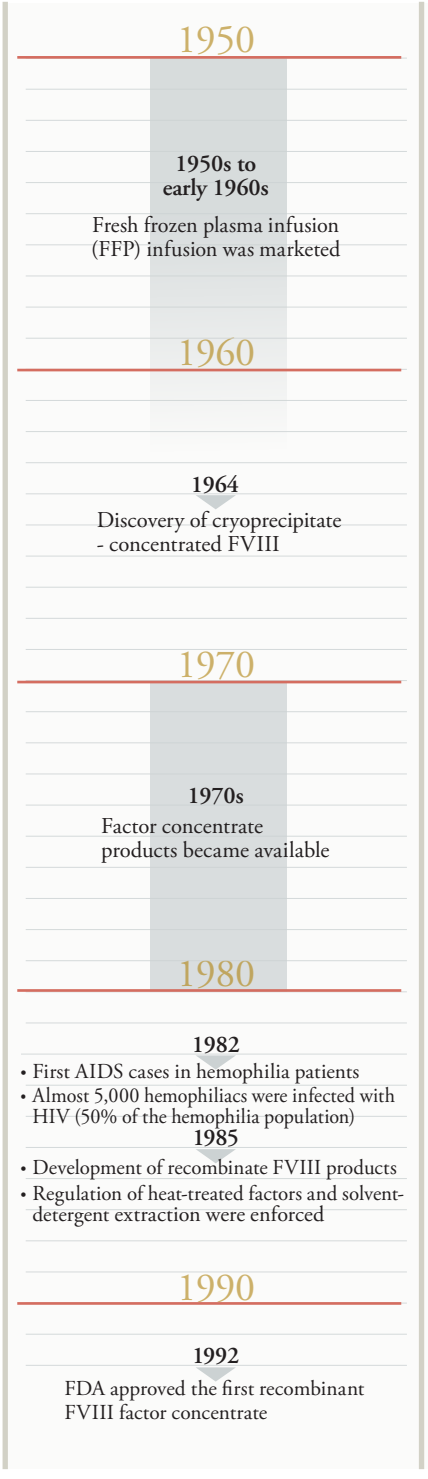
Between the late 1950s and early 1960s, fresh frozen plasma (FFP) first became available for hemophilia patients in hospital settings. Infusion of FFP faced the challenge of volume overload to obtain the necessary amount of clotting factor at the plasma level. This led to another breakthrough when cryoprecipitate, a concentrated factor VIII, was developed in 1965. Since cryoprecipitate provided concentrated amounts of factor VIII in a smaller volume than fresh frozen plasma (FFP), it became the most popular therapy of choice to control bleeding at that time. By the 1970s, powdered factor VIII concentrates were widely marketed, and self-infusion and home treatment became manageable for hemophiliacs.

However, the revolution of plasma concentrates soon recorded the first transmission of HIV/AIDS cases through contaminated products in 1982. Since then, reportedly, about 5,000 patients with hemophilia have been infected with HIV due to the contamination in the United States. In 1992, the Food and Drug Administration (FDA) approved the first recombinant factor VIII (Figure 1).[5,6]

Remarkably, life expectancy for patients with severe hemophilia rose significantly due to the robust development of plasma infusions. Tragically, a vast population of hemophilia patients were unknowingly infected with human immunodeficiency virus (HIV) from contaminated plasma-derived clotting factors. Soon after, an acquired immunodeficiency syndrome (AIDS) became the leading cause of death for Americans in the 1990s.[7]

In 1982, while HIV/AIDS mortality reached its peak, the Centers for Disease Control and Prevention (CDC) reported several cases of hemophilia A patients with acquired HIV/AIDS who received clotting factors. **Patient 1** started

FIGURE 1
The Evolution of Hemophilia Products



experiencing weight loss, fever, and chest x-ray showed interstitial infiltration, which was associated with pneumonia. A lung biopsy was conducted and revealed *Pneumocystis carinii (P. carinii)*. Unfortunately, patient 1 died after he was treated with sulfamethoxazole and trimethoprim (Bactrim) for 2 weeks. **Patient 2** was noted with fever, oropharyngeal candidiasis, recurrent fever, and dysphagia. He was also diagnosed with *P. carinii* pneumonia and *cytomegalovirus* (CMV). He was given a month-long course of pentamidine and Bactrim until his death. **Patient 3** was diagnosed with *P. carinii* pneumonia, oral candidiasis, and *Mycobacterium avium* (MAC) bacteremia. Fortunately, the patient survived after extensive courses of antibiotics (SMZ/TMP) and antifungal treatment (Ketoconazole).[8]

From late-1982 to early-1983, additional cases of acquired HIV/AIDS in hemophilia A were further recorded. **Patient 4** developed anorexia and progressive weight loss. Hospital readmission revealed transient thrombocytopenia and persistent inversion of the T-helper/T-suppressor ratio (TH/TS=0.2). On his third admission, sputum culture showed *P. carinii*, and the patient survived after a long course of SMZ/TMP. **Patient 5** was noted with 101.2°F fever, thrombocytopenia, elevated serum IgG, IgM, and IgA. Chest x-ray revealed *P. carinii* and rare *Cryptococcus neoformans* pneumonia. Remarkably, the patient clinically improved after an extended treatment of Bactrim and amphotericin B.

Patient 6 had mild hemophilia with relatively infrequent factor VIII concentrate treatment. His admission recorded dysphagia, diaphoresis, and weight loss. The TH/TS ratio was 0.25. A lung biopsy confirmed *P. carinii* pneumonia. The patient died after showing no improvement while on treatment with SMZ/TMP and pentamidine. Lastly, **Patient 7** was recorded with persistent lymphopenia, leukopenia, oral candidiasis, and bone marrow granuloma with rare *Histoplasma capsulatum*. The patient initially improved after being given amphotericin B. Several months later, the patient was re-hospitalized with leukopenia, lymphopenia, and pulmonary infiltration. Biopsies were collected and revealed disseminated *H. capsulatum*. Further results showed that the white cell count was 400 cells/μL, and lymphocytes were absent. Unfortunately, the patient died after treatments failed.[9] (Table 1)

Following the HIV/AIDS epidemic, hemophiliacs who were unknowingly infected with HIV/AIDS filed lawsuits against several pharmaceutical companies over their contaminated factor products. The action accused these companies of lacking safety and screening processes for bloodborne pathogens. The lawsuits asserted that these pharmaceutical companies acquired their plasma pool from high-risk donors such as drug users and prisoners. Unfortunately, the epidemic continued spreading through Latin America, Asia, and Europe in the mid-1990s. Consequently, these companies agreed to pay $640 million as a settlement.[10] Furthermore, Americans demanded a safer system in the manufacturing process for the plasma supply. As a result, this tragedy immediately prompted manufacturers to implement stricter policies and develop another alternative technology, DNA recombinant.

Editor's Note: According to the U.S. Centers for Disease Control and Prevention (CDC), scientists have changed both the classification and the name of *Pneumocystis carinii* since it first appeared in patients with HIV in the 1980s. *P. carinii* was previously classified as a protozoan; *Pneumocystis jirovecii* is now considered a fungus.

Conclusion

We reviewed 7 cases of hemophilia A patients with HIV/AIDS during the early 1980s when AIDS was not yet well understood. Most of these patients received treatment with antibiotics and antifungals for opportunistic infections, but unfortunately, not all of them survived. Since 1985, no new cases of acquired HIV/AIDS in patients with hemophilia A have been reported. The tragic loss of many hemophiliac patients prompted the manufacturing industry to comply with stringent regulations and develop further novel therapies, including recombinant FVIII products.

Literature also reported 2 brothers cases of hemophilia A who acquired HIV/AIDS due to the contamination.[11,12] Before 1985, 2 older brothers were treated with tainted factor VIII products and unknowingly got infected with HIV. Their young brothers had severe hemophilia A with HIV negative at the time of the older brothers' diagnostic period. Unexpectedly, the set of 2 younger brothers were both found HIV positive in 1991 and 1992, respectively. In these 2 cases, medical records revealed that the 2 younger brothers were contaminated with HIV from

TABLE 1 | HIV Infection in Hemophilia A Patients – Literature Review

Patient No.	1	2	3	4	5	6	7
Sex	M	M	M	M	M	M	M
Age	62	59	27	55	10	49	52
Severity of hemophilia	Severe	Severe	Severe	Severe	Severe	Mild	Severe
Hemophilia treatment	Factor VIII concentrate	Factor VIII concentrate	Factor VIII concentrate	Factor VIII concentrate	Factor VIII concentrate	Intermittent factor VIII concentrate	Factor VIII concentrate
Other medical history	Chronic hepatitis	NA	NA	Diabetes mellitus, hepatosplen-omegaly	Healthy	NA	NA
Onset of AIDS	Feb 1981	Oct 1980	Jul 1981	Sep 1981	Sep 1982	1982	Apr 1982
AIDS diagnosis date	Jan 1982	Feb 1982	Oct 1981	Jun 1982	Oct 1982	Nov 1982	Nov 1982
Symptoms	Weight loss, abdominal pain, severe respiratory distress	Weight loss, dysphagia, ulcers, anterior cervical adenopathy	Fever, urinary urgency, extreme lassitude, splenomegaly, anemia, lymphopenia	Anorexia, weight loss	Fever, vomiting, anorexia, fatigue, sore throat, nonproductive cough	Dysphagia, weight loss, cellulitis, dyspnea, diaphoresis	Fever, lympha-denopathy, abdominal pain, lympha-denopathy, abdominal pain, weight loss
Opportunistic infection	*P. carinii*	*P. carinii* CMV Oropharyngeal candidiasis	*P. carinii* CMV Oropharyngeal candidiasis	*P. carinii* Herpes zoster	*P. carinii* C. neoformans	*P. carinii* HSV	Esophageal candidiasis
Labs	NA	NA	NA	Absolute lymphocyte 450/mm^3, elevated LFT, thrombo-cytopenia 63,000/mm^3	Lymphocyte 580/mm^3, platelet 171,000/ mm^3, elevated IgG, IgA and IgM	WBC 11,000/ mm^3, absolute lymphocyte 990/mm^3	Lymphocyte 480/mm^3, WBC 400/mm^3, granulomata
CXR/sputum culture	NA	NA	NA	Bilateral PNA	Bilateral PNA	Diffuse PNA Sputum HSV	Infiltration *H. capsulatum*
TH/TS ratio	NA	Inverted ratio	Inverted ratio	0.2	0.1	0.25	0.1
AIDS treatment	SMZ/TMP	SMZ/TMP Pentamidine	SMZ/TMP Ketoconazole	SMZ/TMP Adenosine arabinoside	SMZ/TMP Amphotericin B	SMZ/TMP Pentamidine	SMZ/TMP Amphotericin B
Outcome	Patient expired after 2 weeks of treatment	Patient expired 7/5/1982	Alive	Alive	Alive	Expired 11/22/1982	Expired 1982

See Editor's Note on page 24.

their older siblings rather than directly from contaminated blood products. As a result, it highlighted the importance of taking necessary precautions to prevent cross-contamination of bloodborne diseases in health care and home settings.

We report a rare case of hemophilia A patient with acquired HIV/AIDS who also suffered from multiple opportunistic infections, consequently followed by the contaminated plasma product tragedy in the 1990s. Our patient further presented hemophilic complications such as GI bleeding, hemophilic arthropathy, and target joint bleeding throughout his life. However, novel therapies and advanced medical technologies continue to evolve and improve their quality of life. Thus, gene therapy is expected to be the new groundbreaking management for hemophilia. Additionally, other innovative treatments, including anti-tissue factor pathway inhibitors and RNA interference therapy targeting antithrombin, are being explored as potential futuristic treatments.[13]

Abbreviation Key

PNA	pneumonia
CXR	chest x-ray
TH/TS	T-helper/T-suppressor lymphocyte
P. carinii	*Pneumocystis carinii*
C. neoformans	*Cryptococcus neoformans*
H. capsulatum	*Histoplasma capsulatum*
HSV	herpes simplex virus
CMV	cytomegalovirus
SMZ/TMP	sulfamethoxazole and trimethoprim

References

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the Management of Hemophilia. *Haemophilia*. (2013).19(1):e1-47.
2. Castaman G, Matino D. Hemophilia A and B: Molecular and Clinical Similarities and Differences. *Haematologica*. (2019).104(9):1702-1709.
3. Inserro A. Prevalence of hemophilia worldwide is triple that of previous estimates, new study says. *Am J Manag Care*. Updated September 9, 2019. Accessed November 19, 2023. https://www.ajmc.com/view/prevalence-of-hemophilia-worldwide-is-triple-that-of-previous-estimates-new-study-says-
4. Soucie JM, Monahan PE, Kulkarni R, et al. The Frequency of Joint Hemorrhages and Procedures in Nonsevere Hemophilia A vs B. *Blood Adv.*(2018). 2(16):2136-2144.
5. White GC. Hemophilia: An Amazing 35-Year Journey from the Depths of HIV to the Threshold of Cure. Trans Am Clin Climatol Assoc.(2010).121:61-73; discussion 74-65.
6. Bleeding disorders history: 2 AD to modern advances. National Hemophilia Foundation. Accessed November 19, 2023. https://www.hemophilia.org/bleeding-disorders-a-z/overview/history
7. Hay C, Nissen F, Pipe S. Mortality in Congenital Hemophilia A - A Systematic Literature Review. *J Thromb Haemost.*(2021).19 Suppl 1(Suppl 1):6-20.
8. CDC. Epidemiologic notes and reports pneumocystis carinii pneumonia among persons with hemophilia A. *MMWR*. 1982;31(27): 365-7.
9. CDC. Update on acquired immune deficiency syndrome (AIDS) among patients with hemophilia A. *MMWR*. 1982;31(48): 644-6, 652.
10. Josefson D. Haemophilia Patients Launch Action against Bayer over Contaminated Blood Products. *BMJ*. (2003).326(7402):1286.
11. CDC. HIV infection in two brothers receiving intravenous therapy in hemophilia. *MMWR*. 1992;41(14);228-231.
12. CDC. HIV transmission between two adolescent brothers with hemophilia. *MMWR*. 1993;42(49).
13. Exploring future therapies for bleeding disorders. National Hemophilia Foundation. Accessed November 19, 2023. https://www.hemophilia.org/bleeding-disorders-a-z/treatment/future-therapies