The intriguing association between cancer and congenital bleeding disorders

Ezio Zanon

Haemophilia Center, Clinica Medica 1°, Department of Medicine, University Hospital of Padua, Italy

Dear Editor,

The relationship between congenital bleeding disorders and cancer is complex and multifactorial. Some disorders, such as hemophilia, can increase the risk of developing certain cancers.[1] In von Willebrand disease (VWD), solid tumors and lymphoproliferative disorders are reported, but their association with cancer is still not well-established.[2,3] No data are available for other rarer conditions (*e.g.*, FVII, FXIII, or platelet function disorders). Hemophilia patients may have an increased risk of liver cancer and Hodgkin's disease due to chronic inflammation and cell damage from repeated bleeding episodes and replacement therapy.[4] Historically, hemophilia treatment involved plasma-derived products, posing significant risks of contracting Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV), especially before the development of recombinant clotting factors.[5] In the seventies and eighties, many hemophilia patients were treated with plasma-derived products, some of which were contaminated, leading to HIV and HCV infections and serious health complications.[6] These infections had severe consequences, including Acquired Immune Deficiency Syndrome (AIDS) and chronic hepatitis C, and increased cancer risks, such as non-Hodgkin's lymphomas and hepatocellular carcinomas (HCC).[6-12] Miesbach *et al.* found that older adults with HIV had a four times higher cancer prevalence than the general population, excluding HCC.[13] The incidence of HCC is notably higher in hemophilia patients, primarily due to HCV infection, necessitating regular liver disease screening and a multidisciplinary treatment approach.[6,7] Indeed, cirrhosis is also a risk factor associated with HCC for patients with hemophilia. In particular, the incidence of HCC was found to be 3.2 per 100,000 patient/years, 30 times higher than in the general population.[14] Patients with cirrhosis from any etiology are at high risk for HCC, with an annual incidence ranging from 1% to 4%.[15] Excluding virus-related factors, the literature presents conflicting results on cancer mortality in hemophilia patients.[7] Huang *et al.* conducted a nationwide analysis of cancer occurrence and survival in patients with hemophilia (PWH) from 1997 to 2010. They found that PWH had a higher cancer incidence, including hepatocellular carcinoma, than the general population. Still, the survival times were similar to those of the general population after cancer diagnosis.[16] The incidence and survival of cancers among PWH in Taiwan are increasingly affected by age-related diseases. Darby *et al.* found that mortality from liver cancer and Hodgkin's disease was significantly higher in the UK hemophilia population compared to the general population, with no increased mortality from other cancers.[4] In 2021, Hassan *et al.* reported improved survival rates for hemophilia patients in the Netherlands, but still lower than the general population (SMR: 1.4).[17] Previously, a Dutch cohort study found that malignant neoplasms accounted for 22% of deaths from 1992 to 2001, with a high risk of death from hepatocellular carcinoma (SMR: 1.5).[18] The Italian Association of Hemophilia Centers (Associazione Italiana Centri Emofilia - AICE) survey indicated that non-virus-related cancers are less common in severe hemophilia patients than in milder forms.[5] From 2001 to 2018, non-hepatic malignancies (26%) and intracranial bleeding (14%) were frequent causes of death in hemophilia patients, while AIDS (2%), chronic liver disease (7%), and HCC (7%) were less frequent.[17]

As the life expectancy of PWH rises, they face an increased risk of age-related conditions, including cancer. While PWH generally does not have a higher cancer risk than the general population, those with HIV or hepatitis infection may face elevated risks. Patients with congenital bleeding disorders often undergo hemostatic therapies that can influence tumor risk. However, long-term

Correspondence: Ezio Zanon, Hemophilia Center, University Hospital of Padua, Via Giustiniani, 35128 Padua, Italy. Tel.+39.049.8212666. E-mail: ezio.zanon@unipd.it

Contributions: EZ developed the concept, collected the related papers, and wrote the paper.

Conflict of interest: the author declares no conflict of interest.

Informed consent: not applicable.

Availability of data and materials: the data presented in this study are available on request from the author.

Key words: Hemophilia; cancer; malignancy; congenital bleeding disorders.

Received: 9 July 2024.
Accepted: 4 November 2024.

Licensee PAGEPress, Italy
Bleeding, Thrombosis and Vascular Biology 2024; 3:146
doi:10.4081/btvb.2024.146

clotting factor concentrate treatment can intensify thrombin-induced metastases, or replacement dosages may be too low to generate such an effect.[16] Hemophilia treatments, particularly blood transfusions and clotting factor replacement therapy, may increase cancer risk due to exposure to blood products.[19] Anticoagulants have been studied for their potential anticancer effects.[20,21] Experimental *in vitro* studies, such as those by Bruggemann *et al.* and Langer, using a mouse model of hemophilia A, showed that factor VIII replacement increased lung metastases. At the same time, thrombin inhibitors reduced it, highlighting thrombin's role in tumor spread.[22,23] In patients with cancer and congenital bleeding disorders, regular screenings and coordinated care involving hematologists, oncologists, and other specialists are crucial for optimal health management. Survival outcomes depend on factors such as age, early diagnosis, treatment choices, and effective management of bleeding disorders.

Careful evaluation by specialists is essential for any invasive procedures or chemotherapy in PWH with cancer to minimize bleeding risks. Integrating personalized treatments and collaborative care models is vital to optimize management strategies and enhance patient well-being. Early cancer detection is crucial for better prognosis and reduced mortality, and prophylaxis is recommended for patients not already on it to mitigate bleeding risks during treatments. Although the average age of life cancer diagnoses in hemophilia increases,[24] there is no evidence of an increased incidence of malignancies in hemophilia patients compared to the general population. The hypothesis that severe congenital bleeding disorders may protect against cancer is intriguing but remains unproven and requires further investigation.

References

1. Liu CJ, Yu YB, Teng CJ, et al. Increased cancer risk in patients with haemophilia A: a nationwide population-based 14-year study in Taiwan. Haemophilia 2014;20:741–6.
2. Colonne CK, Favaloro EJ, Pasalic L. The intriguing connections between von Willebrand factor, ADAMTS13 and cancer. Healthcare (Basel) 2022;10:557.
3. Franchini M, Di Perna C, Santoro C, et al. Cancers in patients with von Willebrand disease: a survey from the Italian Association of Haemophilia Centres. Semin Thromb Hemost 2016;42:36–41.
4. Darby SC, Kan SW, Spooner RJ, et al. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. Blood 2007;110:815–25.
5. Tagliaferri A, Di Perna C, Santoro C, et al. Cancers in patients with hemophilia: a retrospective study from the Italian Association of Hemophilia Centers. J Thromb Haemost 2012;10:90–5.
6. Shetty S, Sharma N, Ghosh K. Epidemiology of hepatocellular carcinoma (HCC) in hemophilia. Crit Rev Oncol Hematol 2016;99:129–33.
7. Zanon E, Porreca A, Simioni P. Haemophilia and cancer: a literature review. J Clin Med 2024;19;13:1770.
8. Lee CA. The natural history of HIV disease in haemophilia. Blood Rev 1998;12:135–44.
9. Franchini M, Tagliaferri A, Rossetti G, et al. The Natural History of Hepatitis C Virus Infection in Hemophiliacs. Hematology 2001;6:135–42.
10. Franchini M. Haemophilia and cancer: a personal perspective. Blood Transfus 2013;11:26-31.
11. Ragni MV, Belle SH, Jaffe RA, et al. Acquired immunodeficiency syndrome-associated non-Hodgkin's lymphomas and other malignancies in patients with hemophilia. Blood 1993;81:1889–97.
12. Darby SC, Ewart DW, Giangrande PL, et al. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. Lancet 1997;350:1425–31.
13. Miesbach W, Seifried E. Does haemophilia influence cancer-related mortality in HIV-negative patients? Haemophilia 2010;17:55–60.
14. Colombo M, de Franchis R, Del Ninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med 1991;325:675–80.
15. Altekruse SF, Henley SJ, Cucinelli JE, et al. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. Am J Gastroenterol 2014;109:542–53.
16. Huang YC, Tsan YT, Chan WC, et al. Incidence and survival of cancers among 1,054 hemophilia patients: a nationwide and 14-year cohort study. Am J Hematol 2015;90.
17. Hassan S, Monahan RC, Mauser-Bunschoten EP, et al. Mortality, life expectancy, and causes of death of persons with hemophilia in the Netherlands 2001–2018. J Thromb Haemost 2021;19:645–53.
18. Plug I, Van Der Bom JG, Peters M, et al. Mortality and causes of death in patients with hemophilia, 1992–2001: a prospective cohort study. J Thromb Haemost 2006;4:510–6.
19. Franchini M, Lippi G, Montagnana M, et al. Hemophilia and cancer: A new challenge for hemophilia centers. Cancer Treat Rev 2009;35:374–7.
20. Tagalakis V, Tamim H, Blostein M, et al. Use of warfarin and risk of urogenital cancer: a population-based, nested case-control study. Lancet Oncol 2007;8:395–402.
21. Kakkar AK, Levine MN, Kadziola Z, et al. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). J Clin Oncol 2004;22:1944–8.
22. Brüggemann LW, Versteeg HH, Niers TM, et al. Experimental melanoma metastasis in lungs of mice with congenital coagulation disorders. J Cell Mol Me 2008;12:2622–7.
23. Langer F, Amirkhosravi A, Ingersoll SB, et al. Experimental metastasis and primary tumor growth in mice with hemophilia A. J Thromb Haemost 2006;4:1056–62.
24. Dolan G. The challenge of an ageing haemophilic population. Haemophilia 2010;16:11–6.