Annals of Hematology (2022) 101:1861–1863
https://doi.org/10.1007/s00277-022-04819-6

LETTER TO THE EDITOR

Acquired hemophilia A following allogeneic stem cell transplantation for acute lymphoblastic leukemia

Kelsey Uminski[1] · Roy Khalife[1] · Natasha Kekre[1] · Alan Tinmouth[1]

Received: 1 March 2022 / Accepted: 13 March 2022 / Published online: 21 March 2022

Dear Editor,

Acquired hemophilia A (AHA) is a potentially life-threatening bleeding disorder characterized by neutralizing autoantibodies to coagulation factor VIII (FVIII) [1]. AHA may be primary or secondary to conditions such as autoimmune disorders, malignancies [2, 3], and pregnancy [4]. The European Group for Blood and Marrow Transplantation has reported several cases of AHA following autologous hematopoietic stem cell transplantation (HSCT) [5]; however, reports in allogeneic (allo-) HSCT are few [6, 7]. AHA occurring in the context of allo-HSCT presents a unique challenge to the clinician to eradicate the inhibitor while concurrently preserving the graft. Herein, we present a case of AHA following allo-HSCT for acute lymphoblastic leukemia (ALL), with a very high titer inhibitor and severe bleeding phenotype necessitating prophylactic therapy with bypassing agents and then emicizumab, while ongoing immunosuppression was tailored for inhibitor eradication.

A 41-year-old gentleman with a history of T-cell ALL, in remission over 600 days following allo-HSCT, presented with new spontaneous bruising and a large lower extremity hematoma. The patient had undergone a 10/10 matched related donor HSCT, with a conditioning regimen of cyclophosphamide and total body irradiation and concurrent antithymocyte globulin, tacrolimus, and methotrexate as prophylaxis for graft-versus-host disease (GVHD). The patient had been off immunosuppression for 80 days, tapered off slowly due to chronic cutaneous and ocular GVHD. The patient's posttransplant course had been significant for the development of thyroiditis, presumed to be allo- or autoimmune in etiology, manifesting with clinical hyperthyroidism at day 450, followed by hypothyroidism necessitating long-term thyroid hormone replacement. At this same time, the patient was diagnosed with central adrenal insufficiency.

On presentation, the patient had evidence of an isolated prolonged activated partial thromboplastin time (PTT) of 53 s (range 19–28). FVIII activity resulted at < 0.01 U/mL (range 0.50–1.49), and FVIII inhibitor titer was 112 Bethesda unit/mL. von Willebrand antigen and activity levels were 3.00 U/mL (range 0.40–1.75) and 2.54 U/mL (range 0.45–1.80), respectively. The patient received activated prothrombin complex concentrate (aPCC) to manage his bleed and prednisone 1 mg/kg for inhibitor eradication. A CT of the chest/abdomen/pelvis demonstrated no evidence of occult malignancy. Bone marrow biopsy confirmed a morphologic remission, with normal trilineage hematopoiesis. Unfortunately, 1 week following initial discharge, the patient returned with a spontaneous hematoma to the right gastrocnemius muscle treated again with aPCC. His FVIII activity remained undetectable with a FVIII inhibitor at 102 BU/mL (Fig. 1). The decision was to proceed with weekly rituximab administration (4×375 mg/m^2) to eradicate the inhibitor, in addition to continued prednisone. Despite decline in FVIII inhibitor titer following rituximab therapy (Fig. 1), the patient continued to experience additional bleeding events including spontaneous Achilles tendon and gluteus medius hematomas. As initial prophylaxis, the patient was started on recombinant FVIIa prophylaxis (90 mcg/kg daily). An additional hospitalization with a tensor fasciae latae hematoma, despite adherence to rFVIIa, prompted transition to emicizumab. Emicizumab was administered at 3 mg/kg subcutaneously weekly × 4 weeks, followed by 1.5 mg/kg weekly, with no bleeding reoccurrence. Throughout this treatment period, the FVIII inhibitor titer continued to decrease (Fig. 1). Ten weeks following rituximab receipt, FVIII inhibitor remained elevated at 20 BU/mL, with undetectable FVIII activity, prompting the initiation of cyclophosphamide 750 mg/m^2 to eradicate his inhibitor. Following a single dose of cyclophosphamide, the patient was hospitalized with febrile neutropenia with multifocal infections,

✉ Kelsey Uminski
keuminski@toh.ca

[1] Division of Hematology, Department of Medicine, University of Ottawa, Ottawa, ON K1H 8L6, Canada

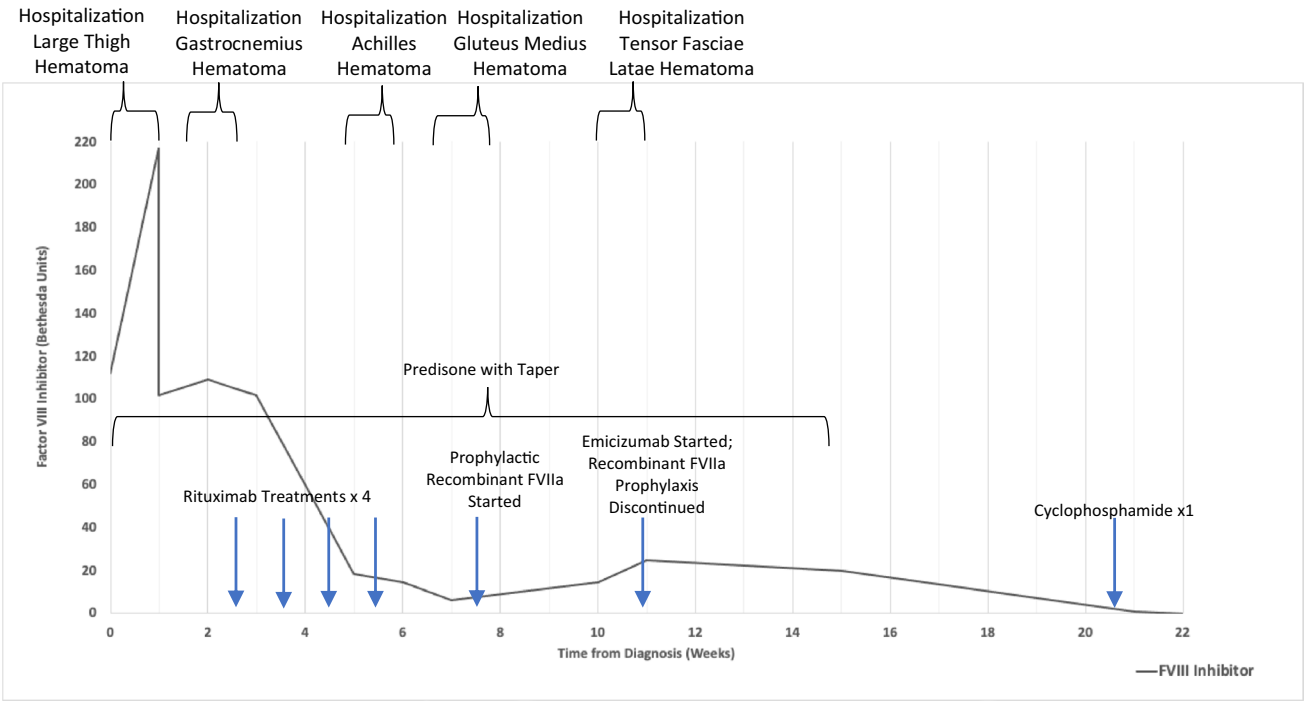

Fig. 1 Trajectory of factor VIII (FVIII) inhibitor in relation to time of diagnosis and treatment receipt

including respiratory syncytial virus, coronavirus Oc43, and scrotal cellulitis. Chromogenic FVIII activity was 0.20 U/mL, with FVIII inhibitor of 1 BU 2 days following receipt of cyclophosphamide, with repeat testing 2 weeks later revealing normalization of chromogenic FVIII activity to 0.90 U/mL, with undetectable FVIII inhibitor. Emicizumab was discontinued due to remission of AHA. Cyclophosphamide was not continued given the severity of febrile neutropenia and continued absence of FVIII inhibitor. Five weeks following AHA diagnosis, and completion of three of four planned rituximab treatments, the patient was noted to be neutropenic. A repeat bone marrow demonstrated no evidence of ALL relapse, with a mild to moderately hypocellular bone marrow with reduced granulopoiesis. Investigations demonstrated full donor CD34 myeloid and CD3 T-cell chimerism. Due to persistence of neutropenia, the patient was started on filgrastim with normalization of his neutrophil count.

In contrast to prior reports of AHA occurring in the context of allo-HSCT, our patient presented with a very high titer inhibitor and severe bleeding phenotype, with delayed response to inhibitor eradication therapy. In contrast to a prior report of AHA occurring following allo-HSCT with cyclosporine exposure, promptly improving with discontinuation [7], our patient was off immunosuppression at the time of diagnosis. Eventually, inhibitor eradication was observed at almost 21 weeks following diagnosis and institution of immunosuppressive therapy with prednisone and rituximab. Median time to inhibitor eradication with the combination of prednisone and rituximab had been reported to be 49 days in a general cohort of patients with AHA [8]. The occurrence of both thyroid and adrenal dysfunction arising in the post-transplant period, and preceding patient clinical presentation with AHA, suggests an immune-mediated phenomena related to transplant. The occurrence of autoimmune disorders post-HSCT has been well documented [9] and in fact is more likely alloimmune from donor cells in the context of full donor chimerism. The immune conditions best described include cytopenias and thyroid disease [9, 10], both of which our patient had. Despite increasing recognition of immune dysregulation posttransplant, the mechanism for this is not well elucidated, nor the homology with the much better described and studied mechanisms for GVHD [9, 10]. The possibility of mismatched FVIII haplotypes between donor and recipient has been speculated as a potential contributor to inhibitor development [6].

Although a rise in FVIII level was observed several days following cyclophosphamide receipt, this was felt to be too early to be attributable to the cyclophosphamide receipt and more likely either a delayed response to the initial immunosuppressive therapy or wane in the immunologic-mediated mechanism underpinning the AHA. Furthermore, the severe bleeding phenotype of this patient prompted the need for prophylactic therapy, while treatment tailored to inhibitor eradication was attained. Emicizumab proved to be effective with resultant cessation of spontaneous bleeding. Demonstrable efficacy has reported in other cases of AHA [11];

however, emizicumab has not been approved for use in AHA and was used off-label. While cyclophosphamide is used in the posttransplant setting, largely for GVHD prophylaxis, the frequency of infections and resultant morbidity are not insignificant [12]. The occurrence of multifocal viral and bacterial infections was demonstrated in our patient following a single dose. As the inhibitor was eradicated, further exposure was not required, mitigating further toxicity. Clinicians should be aware of the potential for uncommon immune-mediated disorders including AHA following allo-HSCT. This case serves to demonstrate successful management of bleeding using emicizumab and subsequent inhibitor eradication, which requires careful consideration in choice of immunosuppression both to preserve graft function and ensure no excess toxicity.

Author contribution Each author was involved in the writing of the manuscript. All authors approved the final manuscript.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from the participating patient of the case description.

Conflict of interest The authors declare no competing interests.

References

1. Tiede A, Collins P, Knoebl P et al (2020) International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica 105(7):1791–1801. https://doi.org/10.3324/haematol.2019.230771
2. Knoebl P, Marco P, Baudo F et al (2012) Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb Haemost 10(4):622–631. https://doi.org/10.1111/j.1538-7836.2012.04654.x
3. Napolitano M, Siragusa S, Mancuso S, Kessler CM (2018) Acquired haemophilia in cancer: a systematic and critical literature review. Haemophilia 24(1):43–56. https://doi.org/10.1111/hae.13355
4. Tengborn L, Baudo F, Huth-Kühne A et al (2012) Pregnancy-associated acquired haemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. BJOG 119(12):1529–1537. https://doi.org/10.1111/j.1471-0528.2012.03469.x
5. Daikeler T, Labopin M, Di Gioia M (2011) Secondary autoimmune diseases occurring after HSCT for an autoimmune disease: a retrospective study of the EBMT autoimmune disease working party. Blood 118(6):1693–1698. https://doi.org/10.1182/blood-2011-02-336156
6. Lozier JN, Nghiem K, Lee M et al (2014) Acquired haemophilia A after stem cell transplant for sickle cell disease: treatment with recombinant porcine factor VIII (OBI-1) and tolerance induction with rituximab/prednisone. Haemophilia 20(2):e185–e188. https://doi.org/10.1111/hae.12372
7. Fan Z, Liu Q, Sun J (2014) Acquired haemophilia A after allogeneic stem cell transplant for acute myeloid leukemia: occurred during cyclosporin a used for chronic graft versus host disease and tolerance induction with rituximab. Blood 124(21):5069. https://doi.org/10.1182/blood.V124.21.5069.5069
8. Collins P, Baudo F, Knoebl P et al (2012) Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Blood 120(1):47–55. https://doi.org/10.1182/blood-2012-02-409185
9. Holbro A, Abinun M, Daikeler T (2012) Management of autoimmune diseases after haematopoietic stem cell transplantation. Br J Haematol 157(3):281–290. https://doi.org/10.1111/j.1365-2141.2012.09070.x
10. Daikeler T, Tyndall A (2007) Autoimmunity following haematopoietic stem-cell transplantation. Best Pract Res Clin Haematol 20(2):349–360. https://doi.org/10.1016/j.beha.2006.09.008
11. Thomas VM, Abou-Ismail MY, Lim MY (2022) Off-label use of emicizumab in persons with acquired haemophilia A and von Willebrand disease: a scoping review of the literature. Haemophilia 28(1):4–17. https://doi.org/10.1111/hae.14450
12. Irene GC, Albert E, Anna BV et al (2021) Patterns of infection and infectious-related mortality in patients receiving post-transplant high dose cyclophosphamide as graft-versus-host-disease prophylaxis: impact of HLA donor matching. Bone Marrow Transplant 56:818–827. https://doi.org/10.1038/s41409-020-01092-x