Letter to the Editor

iMedPub Journals
www.imedpub.com

Journal of Blood Research

2018
Vol.1 No.1:1

Managing a Rare Brain Tumor in a Hemophilia Patient: A Two-Faced Janus on the Coagulation Side

Marta Milan[1], Samantha Pasca[1*], Lucia Sarolo[1], Alessandro Della Puppa[2] and Ezio Zanon[1]

[1]Hemophilia Center, University Hospital of Padua, Italy

[2]Department of Neurosurgery, University Hospital of Padua, Italy

***Corresponding author:** Samantha Pasca, Hemophilia Center, University Hospital of Padua Via Giustiniani, Padua, Italy, Tel: +39-049-8212175; E-mail: sampasca@alice.it

Received date: February 03, 2018; **Accepted date:** February 15, 2018; **Published date:** February 19, 2018

Copyright: © 2018 Mian M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Citation: Milan M, Pasca S, Sarolo L, Puppa AD, Zanon E (2018) Managing a Rare Brain Tumor in a Hemophilia Patient: A Two-Faced Janus on the Coagulation Side. J Blood Res. Vol.1 No.1:1.

Letter to the Editor

Neurosurgical procedures in patients affected by hemophilia represent a complex challenge that involves a multidisciplinary team. Even in patients with normal hemostasis, brain surgery may be responsible for major bleeding. Moreover, these surgical procedures also carry a high risk of venous thromboembolism which makes a hemostatic balance very difficult to maintain. In patients with hemophilia (PWH), the problem of cerebral bleeding is more relevant, and a conservative approach is often suggested whenever possible. The literature contains only few reports of neurosurgeries carried out in PWH, all summarized in **Table 1** [1-10]. Six of these patients received anti-hemorrhagic therapy as a continuous infusion of FVIII, two cases received intravenous therapy with bolus injections of FVIII concentrates, whereas two patients presented inhibitors, so the anti-hemorrhagic therapy was carried out with recombinant FVII activated. All these neurosurgical procedures resulted in a positive outcome without causing permanent neurological deficits. Two cases developed hemorrhagic complications, one of which a small intracranial bleed on postoperative day 7 despite adequate anti-hemorrhagic coverage and the other one a small re-bleed at the site of arterio-venous malformation resection; both cases were promptly resolved by adjusting the anti-hemorrhagic treatment.

Table 1 Summary of published reports on neurosurgical procedures in hemophilic patients. AVM, arterio-venous malformation; BDDrFVIII, B-deleted recombinant factor VIII; CPH, cyclophosphamide; pdFVIII, plasma-derived factor VIII; RAPA, rapamycin; rFVIII, recombinant factor VIII; rFIX, recombinant factor IX; RTX, rituximab.

Author	Type of surgery	Type of hemophilia	Anti-hemorrhagic treatment	Duration of treatment	Hemorrhagic complications
Aouba et al. [1]	Right temporo-parietal glioblastoma resection in an adult patient	Severe hemophilia A with high-titer inhibitor	rFVIIa bolus injections and rituximab	15 days of bolus injections of 270–180 µg/kg rFVIIa every 3 hours, RTX 1000 mg every 12 hours for 14 days	None
Balak et al. [2]	Drainage of a right temporo-parietal-occipito subdural hematoma in a pediatric patient	Moderate hemophilia A	FVIII bolus injections	1 day of bolus injections of 60 IU/kg every 8 hours, 7 days of 60 IU/kg every 12 hours, and another 7 days of 60 IU/kg a day	None
Banov et al. [3]	Drainage of a spontaneous right frontal haematoma in a paediatric patient	Severe haemophilia A with high-titre inhibitor	rFVIIa bolus injections, CPH and RAPA	4 days of bolus injections of rFVIIa 350 µg/kg every 2 hours (60 mg/day), then tapered to 214 µg/kg every 12 hours for 100 days, CPH 10 mg/kg 5 doses, RAPA 3 mg/m2	Small re-bleed on post-operative day 6
Cermelj et al. [4]	Drainage of a spontaneous intra-parenchymal and subdural brain hematoma of the left temporal lobe in a pediatric patient	Severe hemophilia A	Continuous infusion of FVIII followed by bolus injections	10 days of continuous infusion, initially at a dosage of 117 IU/kg day then tapered to 50 IU/kg day, then bolus injections for 10 days	None

Dönmez et al. [5]	Brain aneurysm resection in an adult patient	Hemophilia A	Continuous infusion of rFVIII followed by bolus injections	48 hours of continuous infusion, then bolus injections for 14 days	None
Hanrahan et al. [6]	Pituitary adenoma resection in a pediatric patient	Severe hemophilia A with subsequent low-titer inhibitor development	Continuous infusion of BDDrFVIII followed by bolus injections	14 days of continuous infusion, initially at 120 IU/kg daily and subsequently tapered, followed by 75 IU/kg/day bolus injections for 2 weeks and then 50 IU/kg/day for 3 months	None
Nakau et al. [7]	AVM with epidural hematoma resection in an adult patient	Mild hemophilia A	Continuous infusion of pdFVIII followed by bolus injections	10 days of continuous infusion with 4500 IU daily then bolus injections for 18 days	Small intracranial hemorrhage after 7 days
Saito et al. [8]	Resection of an AVM with left fronto-parietal hemorrhage in an adult patient	Hemophilia A	Continuous infusion of FVIII	10 days of continuous infusion	None
Tabuchi et al. [9]	AVM with right intracerebral parietal hemorrhage resection in an adult patient	Mild hemophilia A	FVIII bolus injections	7 days of 5000 IU/day and then tapered for 7 days	None
Yamamoto et al. [10]	Resection of arachnoid cyst in a pediatric patient	Severe hemophilia B	Continuous infusion of rFIX	7 days of continuous infusion of rFIX	None

We want to add a new case of oligodendrioma management in a patient affected by hemophilia A. The peculiarity of this case report is the onset of the disease in a hemophiliac patient, which is an extremely rare event; this cancer does not in fact appear in the Italian and European registries of cancers affecting hemophiliacs [11,12]. This oligodendroglial tumor is a fortuitous case of cerebral neoplastic disease in PWH, not previous described in literature.

A young man with mild hemophilia A (FVIII:C 15.4%) and a previous hemorrhagic history of epistaxis, gingival bleeding, and major bleeds following traumas, came to our attention following the appearance of dysgeusia, altered vision and a tonic-clonic seizure. Neurological assessment did not detect any focal neurological alterations. Brain CT showed an extensive mass in the right fronto-basal and temporo-opercular region with mass effect on the right lateral ventricle and minimal leftward midline shift. Further investigation with brain MRI showed an extensive signal alteration in the right fronto-opercular, insular and temporo-polar regions, as well as a small enhancing nodule **(Figure 1)**.

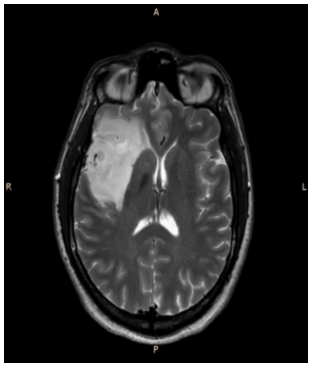

Figure 1 Brain CT scan of the fronto-opercular lesion.

The imaging findings raised a strong suspicion of a glial tumor with high-grade elements with an indication for neurosurgical resection. Subsequent histological examinations confirmed a presence of oligodendroglioma (1p;19q co-deletion, IDH1 mutation, MIB1<5%, grade II). Half an hour before surgery the patient received anti-hemorrhagic treatment with a bolus injection of recombinant FVIII concentrate 55 IU/kg (Helixate NexGen®-CSL Behring) to reach coagulation coverage with plasma FVIII levels of at least 100%. 'Usually, it is recommended to determine a pharmacokinetic curve for FVIII concentrates prior to elective surgery to be able to calculate factor clearance in the individual patient, but in this case the emergency treatment did not allow the pharmacokinetic determination [13]. The FVIII concentrate necessary to achieve the level wanted to guarantee a good homeostasis during surgery was calculated empirically using the recommended formulas and was reached with a single bolus of concentrate [13]. Thirty minutes after the bolus injection, a continuous intravenous infusion of FVIII at an infusion rate of 3 IU/kg/hour or 270 IU/hour and intravenous tranexamic acid 1 g every 8 hours were administered. The plasma FVIII levels were monitored several times on the day of surgery and once a day over the following days. During the first 2 days, the FVIII plasma levels remained above 150% so that on day 3 the infusion rate was decreased to 2.1 IU/kg/hour or 200 IU/hour. This therapy was maintained until postoperative day 7, resulting in adequate levels of coagulation coverage (FVIII constantly greater than 100%). From day 8 to day 10 we maintained the continuous infusion with FVIII 1.8 IU/kg/hour or 166 IU/hour and from day 11 we continued with FVIII bolus injections (1000 IU every 12 hours) for 3 days followed by FVIII 1000 IU daily for another 5 days until final discontinuation. The FVIII plasma levels remained higher than 50% even during this period. Intermittent Pneumatic Compression (IPC) to avoid thromboembolic risk was started immediately after surgery, while an antithrombotic prophylaxis with enoxaparin 4000 IU daily was started from

postoperative day 4. Thromboprophylaxis was stopped at discharge, after 14 days of treatment. The surgery and the postoperative course were not complicated by hemorrhagic or thrombotic events or by the development of FVIII inhibitor. The findings of a postoperative brain CT were consistent with post-resection status without any signs of hemorrhage. The patient was subsequently referred to oncology department for cycles of chemotherapy.

Oligodendrogliomas are rare malignant brain tumors that account for 5–20% of all glial tumors and affect adult patients aged 40–64 years; their incidence is between 0.2 and 0.4 new cases per 100,000 persons per year [14]. They preferentially arise in the cortex and white matter of the cerebral hemispheres, especially in the frontal lobe (involved in up to 50–65% of cases). The signs and symptoms at onset are nonspecific, depending on the grade and location of the tumor. In particular, low-grade oligodendrogliomas tend to present with epileptic seizures, whereas high-grade lesions manifest with focal deficits, intracranial hypertension or early cognitive impairment. Surgical resection is the main treatment for these tumors and is carried out both to ascertain the nature of the lesion and to improve the signs, symptoms and prognosis. The success of the neurosurgical procedure, carried out without any hemorrhagic or thrombotic complication, was the result of close monitoring of the anti-hemorrhagic therapy dosages and FVIII plasma levels. During the first 7 days, the FVIII concentrate was administered as a continuous infusion so as to maintain stationary FVIII levels above 100% and avoid hemorrhagic complications, while paying attention to the risk of thrombosis. This was made possible by brain CT monitoring that ruled out thrombosis of the venous sinuses, the use of IPC and the administration of anticoagulation prophylaxis from day 4 postoperatively to discharge. As of day, 11, the anti-hemorrhagic therapy was switched to bolus injections, treatment sufficient to maintain FVIII levels constantly above 50%. Usually, it is recommended to determine a pharmacokinetic curve for FVIII concentrates prior to surgery, but in this case, it was not possible because of the urgent nature of the neurosurgical procedure. In any case, no consolidated data exist on the clearance of FVIII concentrates in mild hemophilia A patients undergoing neurosurgical procedures, most likely because of the interference of endogenous FVIII production which varies among patients. Consequently, the correct anti-hemorrhagic coverage in patients affected by mild hemophilia A remains debated.

Major surgery in PWH is one of the main current challenges. Because of the potential for increased life expectancy and improved quality of life, PWH can often require surgical procedures, and clinical experience in this regard varies. Neurosurgery in PWH, which is significantly more challenging, requires additional careful attention. On the one hand, even small hemorrhages can result in catastrophic and disabling clinical outcomes, making proper management of the trough levels of FVIII:C essential, while on the other hand, this type of surgery is associated with a very high prothrombotic stimulus and strict monitoring of the FVIII:C peaks is required.

Analysis of these case reports reveals that an adequate continuous intravenous infusion of FVIII concentrates can allow excellent control of plasma FVIII levels, avoiding the unnecessary and harmful peaks that immediately follow the bolus injection and the deep troughs in subsequent hours.

Our patient did not develop a FVIII inhibitor. This complication occurs in around 20–30% of severe hemophilia A patients and in 3–13% of patients affected by mild-moderate hemophilia A undergoing FVIII concentrate infusions [15]. As concerns the role of continuous infusion of FVIII concentrates in inhibitor development, the published data are limited. Among the cases reported in the literature, only one patient developed a low-titer inhibitor following the neurosurgical procedure [6], and the inhibitor subsequently regressed spontaneously without affecting the outcome.

An aspect worthy of note in our case was the use of pharmacological thromboprophylaxis. During the perioperative period in patients affected by hemophilia thromboprophylaxis is not standard. None of the neurosurgical cases described in the literature reports on the use of pharmacological prophylaxis, but its use may be considered when additional risk factors are present. In our case thromboembolic risk was very high because of oncologic neurosurgery, in addition our patient was a mild hemophiliac with a baseline level of FVIII >15% reaching >100% after anti-hemorrhagic therapy, that determine another increase in thrombosis risk. Therefore, we decided to treat him with a pharmacological thromboprophylaxis, as reported in another case of oncologic surgery in patients with mild hemophilia [16].

In conclusion, even major neurosurgical procedures can be performed with a certain degree of confidence and effectiveness in hemophilic patients by administering anti-hemorrhagic therapy with FVIII concentrates as a continuous infusion. Constant monitoring of FVIII plasma levels allows adjustment of FVIII concentrate dosage ensuring adequate coagulation coverage and the use of pharmacological antithrombotic prophylaxis.

The patient has consented to the submission of this case report to the journal.

References

1. Aouba A, Dezamis E, Sermet A, Rothschild C, Hermine O, et al. (2010) Uncomplicated neurosurgical resection of a malignant glioneuronal tumour under haemostatic cover of rFVIIa in a severe haemophilia patient with a high-titre inhibitor: a case report and literature review of rFVIIa use in major surgeries. Haemophilia 16: 54-60.
2. Balak N, Silav G, Kiliç Y, Timur C, Elmaci I (2007) Successful surgical treatment of a hemophiliac infant with nontraumatic acute subdural hematoma. Surg Neurol 68: 537-540.
3. Banov L, Pavanello M, Piattelli G, Disma N, Severino M, et al. (2014) Successful urgent neurosugery management with rFVIIa mega doses in a child with haemophilia A and high titre inhibitor. Blood Coagul Fibrinolysis 25: 518-521.

© Copyright iMedPub

4. Cermelj M, Negro F, Schijman E, Ferro AM, Acerenza M, et al. (2004) Neurosurgical intervention in a haemophilic child with a subdural and intracerebral haematoma. Haemophilia 10: 405-407.

5. Dönmez A, Türker H, Sekerci S, Kayhan Z, Ozbek N (1999) Dealing with a hemophilia-A patient undergoing cerebral aneurysm surgery. J Neurosurg Anesthesiol 11: 214-215.

6. Hanrahan J, McKinnell J, Storrs B, Jones JE, Schwartz M, et al. (2003) Successful use of B-domain deleted factor VIII for resection of pituitary adenoma in a paediatric patient with severe haemophilia A. Haemophilia 9: 650-653.

7. Nakau H, Maruishi M, Takiguchi H, Shima K (1998) Successful surgical removal of a large arteriovenous malformation in a patient with hemophilia: case report. Neurosurgery 43: 1459-1461.

8. Saito N, Yamazaki M, Kobayashi S, Teramoto A (2006) Resection of arteriovenous malformation in a patient with hemophilia type A. Neurol Med Chir 46: 191-193.

9. Tabuchi S, Asaeda M, Kamitani H, Watanabe T (2006) Surgical treatment of arteriovenous malformation in a patient with human immunodeficiency virus infection and hemophilia a: case report. J Stroke Cerebrovasc Dis 15: 66-68.

10. Yamamoto M, Nakadate H, Iguchi U, Masuda H, Sakai H, et al. (2013) Successful management of neurosurgical procedures with continuous infusion of recombinant factor IX in a child with hemophilia B. Rinsho Ketsueki 54: 300-304.

11. Biron-Andreani C, de Moerloose P, D'oiron R, Chambost H, Schved JF, et al. (2014) Cancer detection and management in patients with haemophilia: a retrospective European multicentre study. Haemophilia 20: 78-82.

12. Tagliaferri A, Di Perna C, Santoro C, Schinco P, Santoro R, et al. (2012) Cancers in patients with hemophilia: a retrospective study from the Italian Association of Hemophilia Centers. J Thromb Haemost 10: 90-95.

13. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, et al. (2013) Guidelines for the management of hemophilia. Haemophilia 19: e1-47.

14. Crocetti E, Trama A, Stiller C, Caldarella A, Soffietti R, et al. (2012) Epidemiology of glial and non-glial brain tumours in Europe. Eur J Cancer 48: 1532-1542.

15. Sharathkumar A, Lillicrap D, Blanchette VS, Kern M, Leggo J, et al. (2003) Intensive exposure to factor VIII is a risk factor for inhibitor development in mild hemophilia A. J Thromb Haemost 1: 1228-1236.

16. Barillari G, Pasca S (2012) Continuous infusion of rFVIII:a good choice for mild hemophiliac patient undergoing major oncologic surgery and reconstructive plastic surgery. Chirurgia 25: 84-85.