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

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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 thromboembolism which makes a conservative approach is often suggested whenever possible. The literature contains only few reports of neurosurgery 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.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of surgery</th>
<th>Type of hemophilia</th>
<th>Anti-hemorrhagic treatment</th>
<th>Duration of treatment</th>
<th>Hemorrhagic complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aouba et al. [1]</td>
<td>Right temporo-parietal glioblastoma resection in an adult patient</td>
<td>Severe hemophilia A with high-titer inhibitor</td>
<td>rFVIII bolus injections and rituximab</td>
<td>15 days of bolus injections of 270–160 µg/kg rFVIIIa every 3 hours, RTX 1000 mg every 12 hours for 14 days</td>
<td>None</td>
</tr>
<tr>
<td>Balak et al. [2]</td>
<td>Drainage of a right temporo-parietal-occipito subdural hematoma in a pediatric patient</td>
<td>Moderate hemophilia A</td>
<td>FVIII bolus injections</td>
<td>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</td>
<td>None</td>
</tr>
<tr>
<td>Banov et al. [3]</td>
<td>Drainage of a spontaneous right frontal haematoma in a paediatric patient</td>
<td>Severe haemophilia A with high-titer inhibitor</td>
<td>rFVIIIa bolus injections, CPH and RAPA</td>
<td>4 days of bolus injections of rFVIIIa 350 µg/kg every 2 hours (60 mg/day), then tapered to 214 µg/kg every 12 hours for 100 days, CPM 10 mg/kg 5 doses, RAPA 3 mg/m2</td>
<td>Small re-bleed on post-operative day 8</td>
</tr>
<tr>
<td>Cermelj et al. [4]</td>
<td>Drainage of a spontaneous intra-parenchymal and subdural brain hematoma of the left temporal lobe in a pediatric patient</td>
<td>Severe hemophilia A</td>
<td>Continuous infusion of FVIII followed by bolus injections</td>
<td>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</td>
<td>None</td>
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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 hemophilic patient, which is an extremely rare event; this cancer does not in fact appear in the Italian and European registries of cancers affecting hemophiliaacs [11,12]. This oligodendroglial tumor is a fortuitous case of cerebral neoplastic disease in PWH, not previously 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 temporopolar 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).

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 core-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 (1000 IU every 12 hours).

Until 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Case Description</th>
<th>Hemophilia Type</th>
<th>Management</th>
<th>Duration of FVIII Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dönmez et al. [5]</td>
<td>Brain aneurysm resection in an adult patient</td>
<td>Hemophilia A</td>
<td>Continuous infusion of rFVIII followed by bolus injections</td>
<td>48 hours of continuous infusion, then bolus injections for 14 days</td>
</tr>
<tr>
<td>Hanrahan et al. [6]</td>
<td>Pituitary adenoma resection in a pediatric patient</td>
<td>Severe hemophilia A with subsequent low-titer inhibitor development</td>
<td>Continuous infusion of BDD-FVIII followed by bolus injections</td>
<td>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</td>
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<tr>
<td>Nakau et al. [7]</td>
<td>AVM with epidural hematoma resection in an adult patient</td>
<td>Mild hemophilia A</td>
<td>Continuous infusion of FVIII followed by bolus injections</td>
<td>10 days of continuous infusion for 18 days</td>
</tr>
<tr>
<td>Saito et al. [8]</td>
<td>Resection of an AVM with left fronto-parietal hemorrhage in an adult patient</td>
<td>Hemophilia A</td>
<td>Continuous infusion of FVIII</td>
<td>10 days of continuous infusion</td>
</tr>
<tr>
<td>Yamamoto et al. [9]</td>
<td>Resection of arachnoid cyst in a pediatric patient</td>
<td>Severe hemophilia B</td>
<td>Continuous infusion of rFIX</td>
<td>7 days of continuous infusion of rFIX</td>
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</table>

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


