Gelatin–thrombin Hemostatic Matrix-related Cyst Formation after Cerebral Hematoma Evacuation: A Report of Two Cases

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Abstract

The gelatin–thrombin matrix, Floseal, is an excellent novel hemostatic agent that is used in various surgical fields. Thrombin is a serine protease, and the conversion of prothrombin to thrombin is an essential step in the coagulation cascade. However, thrombin can induce blood–brain barrier (BBB) disruption and vasogenic brain edema. This report describes two cases of gelatin–thrombin matrix-related cyst formation after cerebral hematoma evacuation. An 82-year-old man with a gelatin–thrombin matrix-related cyst was treated by cyst drainage and fenestration to the lateral ventricle. Histological evaluation of the cyst wall showed a gelatin–thrombin matrix reserve, marked infiltration of inflammatory cells, and foam cell accumulation. In addition, an 85-year-old woman with a gelatin–thrombin matrix-related cyst was treated with steroids and responded well. In both cases, the post-treatment course was uneventful. Cyst shrinkage and no recurrence were observed. The gelatin–thrombin matrix can cause cyst formation with brain edema. This is the first report demonstrating the cyst wall pathology and the steroid responsivity on cyst shrinkage. The mechanism of cyst formation is thought to be thrombin-induced BBB disruption. Excess gelatin–thrombin matrix should be carefully removed from the surgical beds, particularly those having a blinded space from the neurosurgical microscope.

Keywords: gelatin–thrombin hemostatic matrix, Floseal matrix, cerebral hemorrhage, blood–brain barrier, cysts

Introduction

The gelatin–thrombin matrix, Floseal, is an excellent novel hemostatic agent that was approved by the Food and Drug Administration in 1999 and covered by the National Health Insurance in Japan in 2014. This hemostatic agent is commonly used in various surgical fields, and its utility has also been reported in the neurosurgical field in the treatment of brain tumor, spine, intracerebral hemorrhage, and intraventricular hemorrhage. However, adverse effects related to the gelatin–thrombin matrix have been reported, such as inflammation, adhesion, granulation, edema, and allergic reactions, including anaphylaxis. Thrombin is a serine protease, and the conversion of prothrombin to thrombin is an essential step in the coagulation cascade. However, thrombin has many additional functions and effects. For example, thrombin facilitates hemostasis after intracerebral hemorrhage. It can be neurotoxic by eliciting DNA fragmentation and can induce blood–brain barrier (BBB) disruption and vasogenic brain edema. Furthermore, thrombin has concentration-dependent effects in the brain; at low concentrations, it elicits neuroprotective effects, but it can result in brain damage at high concentrations. Here, we report two cases of potential gelatin–thrombin matrix-related cyst formation with worsening brain edema and review the literature.
Case Reports

Case 1
An 82-year-old man presented to our hospital with left hemiparesis. Brain computed tomography (CT) revealed a subcortical hemorrhage in the right frontal lobe (hematoma volume: 35 mL) (Fig. 1A). Conservative treatment involving blood pressure reduction was selected because his consciousness was clear. His consciousness gradually decreased to Glasgow Coma Scale (GCS)-E2M5V3 due to brain edema (Fig. 1B). Therefore, a frontoparietal craniotomy and hematoma evacuation were performed on day 7 after admission. After surgery, his consciousness recovered to GCS-E3M6V4. A gelatin–thrombin matrix (Floseal) was used in the hematoma cavity for hemostasis. Irrigation to remove the gelatin–thrombin matrix was performed during surgery. On postoperative day 1, brain CT showed pseudoair hypoattenuation, suggesting the presence of residual gelatin–thrombin matrix (Fig. 1C). His consciousness gradually decreased again to GCS-E1M4V1 on postoperative day 5. Surprisingly, brain CT and magnetic resonance (MR) imaging revealed subfalcine herniation caused by the cyst in the hematoma cavity with worsening brain edema (Figs. 1D and 2A–2E). Emergency cyst drainage and cyst fenestration to the lateral ventricle were performed. Intraoperative findings indicated that a previous corticotomy was closed, and an isolated cavity was formed. Red-brown sterile fluid accumulated in the hematoma cavity, and the cyst wall was composed of whitish areolar tissue (Fig. 2F–2G). Fluid analysis revealed a high protein concentration of 3.9 g/dL (fluid protein/serum protein ratio = 0.81) and high lactate dehydrogenase (LDH) concentration of 7757 U/L (fluid LDH/serum LDH ratio = 24.24). Fluid culture for bacteria was negative. Hemostasis by bipolar coagulation and repeated irrigation were carefully performed. His consciousness recovered to GCS-E4M6V4, and his postoperative course was uneventful. Histological evaluation of the cyst wall revealed gelatin–thrombin matrix residue, inflammatory cell infiltration (Fig. 2H), and foam cell accumulation (Fig. 2I). There was no recurrence of cyst formation with brain edema observed within 90 days postoperatively.

Case 2
An 85-year-old woman presented to our hospital with left hemiplegia. Brain CT revealed subcortical hemorrhage in the right frontal lobe (hematoma volume: 31 mL) (Fig. 3A). Her consciousness was GCS-E3M6V4. Front-parietal craniotomy and hematoma evacuation were performed on day 1 after admission (Fig. 3B). A gelatin–thrombin matrix (Floseal) was used in the hematoma cavity for...
Fig. 2 (A–E) Brain MR imaging on postoperative day 5 demonstrating the cyst in the hematoma cavity. Diffusion-weighted image showing hyperintensity at the cyst wall (A). T1-weighted image showing isointensity (B). T2-weighted image showing hyperintensity (C). Cyst wall enhancement on axial (D) and coronal (E) MR images after gadolinium administration. (F) Intraoperative view indicating the whitish areolar tissue and fluid accumulation in the cyst. (G) Red-brown sterile fluid in the cyst. (H and I) Hematoxylin and eosin staining demonstrating eosinophilic acellular material and infiltration of inflammatory cells (H) and foam cell accumulation (I). Scale bar = 100 µm. MR: magnetic resonance.

Fig. 3 Brain CT on day 1 after admission (A) and postoperative day 1 (B). (C) Brain CT on postoperative day 15 showing the cyst in the hematoma cavity. (D) Brain CT on postoperative day 25 indicating cyst shrinkage after steroid treatment. CT: computed tomography.
hemostasis. Unlike in case 1, careful irrigation was repeated to remove excess gelatin–thrombin matrix in the hematoma cavity. After surgery, her consciousness recovered to GCS-E4M6V4. However, her consciousness gradually decreased again to GCS-E1M4V1 on postoperative day 15. Surprisingly, brain CT (Fig. 3C) and MR imaging (Fig. 4A–4E) revealed cyst formation in the hematoma cavity with worsening brain edema. Fever, meningeal sign, leukocytosis, and C-reactive protein elevation on blood tests were not detected. Overall, brain abscesses were considered negative according to these findings. Intravenous steroid treatment (dexamethasone, 0.06 mg/kg/day) was administered for 3 days, and her consciousness significantly recovered to GCS-E4M6V4. Her medication was switched to oral steroid treatment (dexamethasone, 0.01 mg/kg/day) for an additional 3 days. The cyst appeared to be responsive to steroid treatment on brain CT (Fig. 3D). Brain MR imaging indicated shrinkage of the cyst on postoperative day 25 (Fig. 4F–4J). There was no recurrence of cyst formation observed for 60 days postoperatively.

**Discussion**

We herein report an extremely rare complication of gelatin–thrombin matrix-related cyst formation after cerebral hematoma evacuation.

**Characteristics of gelatin–thrombin matrix-related cyst**

Three reports describing six cases with gelatin–thrombin matrix-related cyst formation have been identified to the best of our knowledge, including the present study. In these six cases, cyst formation was observed from 5 to 15 days after the initial surgery using the gelatin–thrombin matrix. Furthermore, brain CT and MR imaging showed cyst wall enhancement and brain edema. Serosanguineous fluid was accumulated in the cavity using the gelatin–thrombin matrix. Primary diseases were intracerebral hemorrhage (four cases) and brain tumor (two cases). Moreover, the cyst can gradually enlarge and induce brain herniation. Brain abscesses should be ruled out with brain imaging and systemic conditions.

**Mechanisms of gelatin–thrombin matrix-related cyst**

Two mechanisms have been proposed to induce gelatin–thrombin matrix-related cyst formation with brain edema. The first mechanism is thrombin-induced BBB disruption: thrombin can disrupt the BBB and lead to brain edema and fluid collection. The inflammatory cell infiltration of the cyst wall in case 1 and drastic steroid responsivity in case 2 support this hypothesis. The second mechanism is the check valve: cerebrospinal fluid influx from
the ventricle to the isolated space due to gelatin–
thrombin matrix induces fibrosis around the ependymal
layer. However, the second hypothesis is in
disagreement with our results. Analysis of the sterile
cyst fluid in case 1 revealed a high protein level of
3.9 g/dL (fluid protein/serum protein ratio = 0.81)
and a high LDH level of 7757 U/L (fluid LDH.serum
LDH ratio = 24.2). These results met Light’s criteria
to determine exudate. Therefore, we speculate
that the cyst fluid was mainly derived from exudate
due to BBB disruption.

Treatment of gelatin–thrombin matrix-related cyst
In five of the six cases, cyst fluid evacuation (with
or without cysto-ventriculostomy) or drainage were
performed to prevent brain herniation. Importantly,
we first demonstrated that steroid treatment
was significantly effective for cyst shrinkage as well
as brain edema. Steroids have a beneficial effect on
vasogenic edema by stabilizing the capillary endo-
thelial junction and reducing cerebrovascular perme-
ability. Given that thrombin induced BBB disrupt-
ion mechanism and inflammatory cell infiltration
of the cyst wall, steroid administration may be
considered as an initial treatment for gelatin–thrombin
matrix-related cysts. However, prompt surgical
intervention should be performed in cases of
impending brain herniation.

Edema formation after intracerebral hemorrhage
Intracerebral hemorrhage is a medical emergency
with a high mortality and poor functional end results
in its survivors. Hematoma volume is a key factor
affecting outcomes in patients with intracerebral
hemorrhage. Hematoma often expands during the
first 6 hours after symptoms onset. Risk factors for
hematoma expansion, including antiplatelet therapy,
anti-coagulant use, intervals from symptom onset to
emergency arrival, hematoma volume, and spot sign,
have been reported. The effectiveness of minimally
invasive hematoma evacuation has also been reported
in recent years. Brain edema around hematoma
results in more severe and durable brain injury.
The edema formation after intracerebral hemorrhage
has three phases. In the first phase (first few hours),
hydrostatic pressure and clot retraction with serum
from the clot into the surrounding tissue. In
the second phase (first 2 days), the coagulation cascade
is activated, and thrombin induces edema formation
and BBB disruption. In the third phase (on about
day 3), erythrocyte lysis results in the release of
hemoglobin degradation products, including iron,
the extracellular space, contributing to delayed
brain injury.

Combination effect of thrombin and iron on BBB
disruption
Thrombin can be neurotoxic, eliciting DNA
fragmentation, and can induce BBB disruption
and vasogenic edema. Furthermore, the combi-
nation of iron and thrombin can augment its
neurotoxic effect, leading to disruption of the
BBB. In case 1, initial surgery using a gelatin–
thrombin matrix was performed on day 7 after
admission. Erythrocyte lysis may have progressed
more at this point than in the early phase of
hematoma. The combination of progressed eryth-ocyte lysis, including iron and gelatin–thrombin
matrix use, may have contributed to BBB disrupt-
ion and cyst formation.

Prevention of gelatin–thrombin
matrix-related cyst
The gelatin–thrombin matrix demonstrates pseudo-
door hypoattenuation on brain CT within 48 hours
after surgery. Case 1 also exhibited pseudo-door
hypoattenuation on postoperative brain CT, which
may imply insufficient irrigation to remove the
gelatin–thrombin matrix. A small corticotomy is
typically performed in surgery for lobar hemorrhage
on the lesion nearest to the hematoma. A space
blinded to neurosurgical microscopy can exist,
particular if the hematoma extends horizontally
to the cortical surface. Furthermore, thrombin has
concentration-dependent effects on the brain, and
high concentrations induce brain damage.
Therefore, caution should be exerted to ensure no excess
gelatin–thrombin matrix remains in such cases of
lobar hemorrhage. However, careful irrigation could
not prevent cyst formation in case 2. Therefore, this
phenomenon may not be attributed only to a remnant
gelatin–thrombin matrix. Gelatin allergy has also
been reported with the use of the gelatin–thrombin
matrix. Further studies are needed to find the
patients who can progress to gelatin–thrombin
matrix-related cyst formation.

Conclusions
The gelatin–thrombin matrix can cause cyst forma-
tion with brain edema. This is the first report
demonstrating the cyst wall pathology and the
steroid responsivity on cyst shrinkage. The mecha-
nism of cyst formation is thought to be throm-in-induced BBB disruption. Excess gelatin–thrombin
matrix should be carefully removed from the surgical
beds, particularly in cases where there are spaces
blinded from view with the neurosurgical micro-
scope.
Conflicts of Interest Disclosure
The authors declare no conflicts of interest. All authors have registered online Self-reported COI Disclosure Statement Forms through the website for The Japan Neurosurgical Society members.

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