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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,[1–5] and its utility has also been reported in the neurosurgical field in the treatment of brain tumor, spine, intracerebral hemorrhage, and intraventricular hemorrhage.[6–11] However, adverse effects related to the gelatin–thrombin matrix have been reported, such as inflammation, adhesion, granulation, edema, and allergic reactions, including anaphylaxis.[12–17]

Thrombin is a serine protease, and the conversion of prothrombin to thrombin is an essential step in the coagulation cascade.[18] However, thrombin has many additional functions and effects.[19] For example, thrombin facilitates hemostasis after intracerebral hemorrhage. It can be neurotoxic by eliciting DNA fragmentation,[20] and can induce blood–brain barrier (BBB) disruption[21] and vasogenic brain edema.[22,23] 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.[19,24]

Here, we report two cases of potential gelatin–thrombin matrix-related cyst formation with worsening brain edema and review the literature.

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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

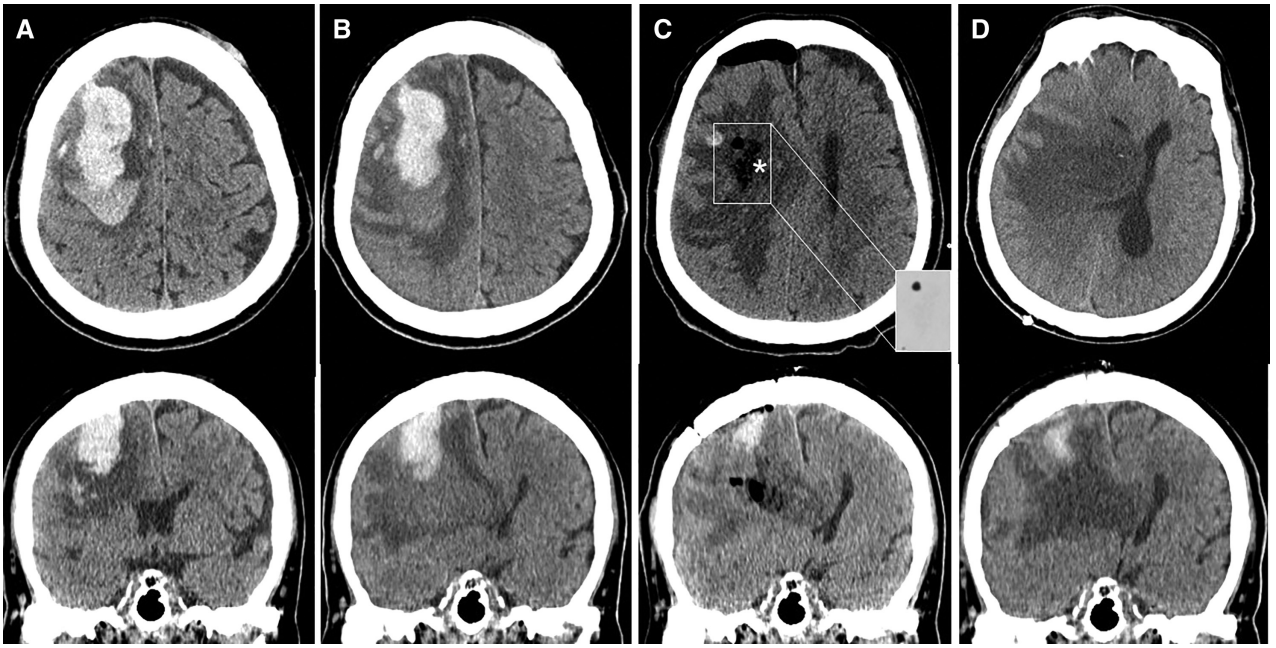

Fig. 1 Brain CT on day 1 (A) and day 7 (B) after admission. (C) Brain CT on postoperative day 1 showing hematoma disappearance and pseudoair hypoattenuation (*) estimated with lung windows (window widths of 1500). (D) Brain CT on postoperative day 5 indicating subfalcine herniation caused by the cyst in the hematoma cavity. CT: computed tomography.

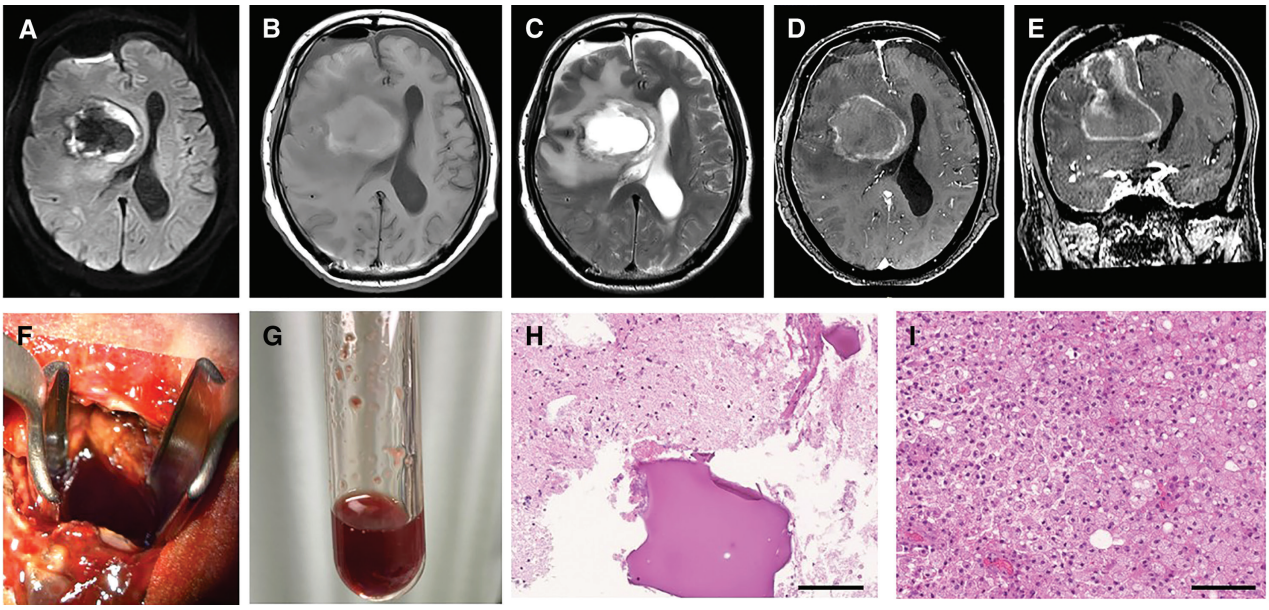

Fig. 2 (A–E) Brain MR imaging on postoperative day 5 demonstrating the cyst in the hematoma cavity. Diffusion-weighted image showing hyperintensity at the cyst wall (A). T1-weighted image showing isointensity (B). T2-weighted image showing hyperintensity (C). Cyst wall enhancement on axial (D) and coronal (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.

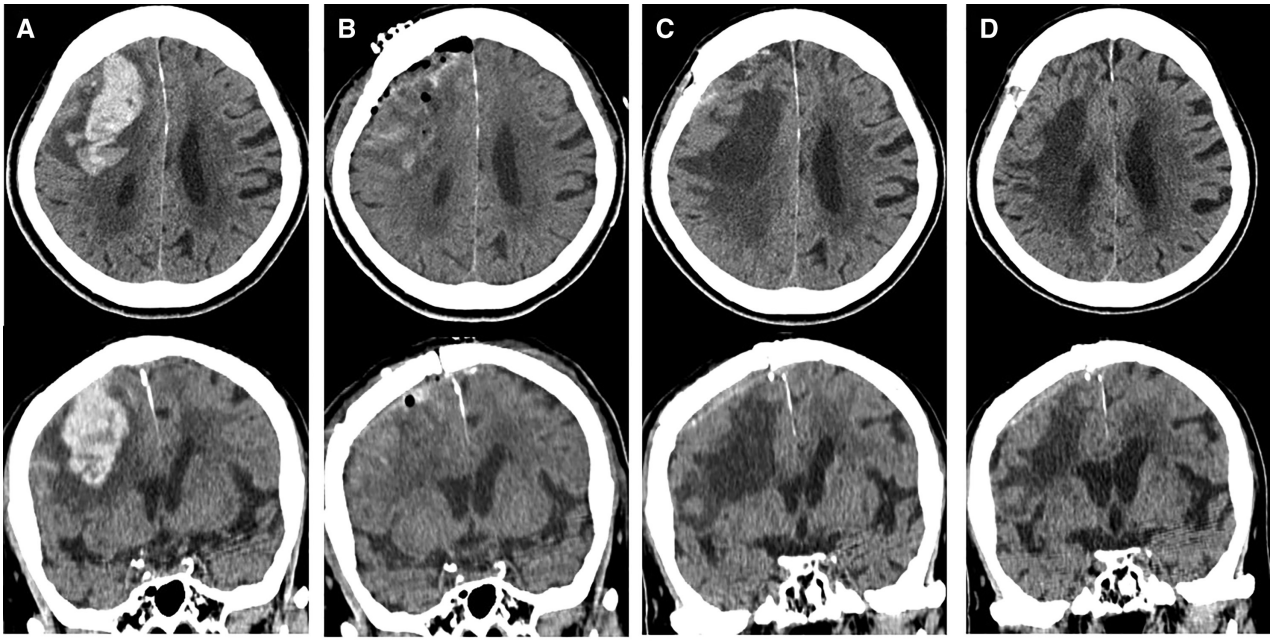

Fig. 3 Brain CT on day 1 after admission (A) and postoperative day 1 (B). (C) Brain CT on postoperative day 15 showing the cyst in the hematoma cavity. (D) Brain CT on postoperative day 25 indicating cyst shrinkage after steroid treatment. CT: computed tomography.

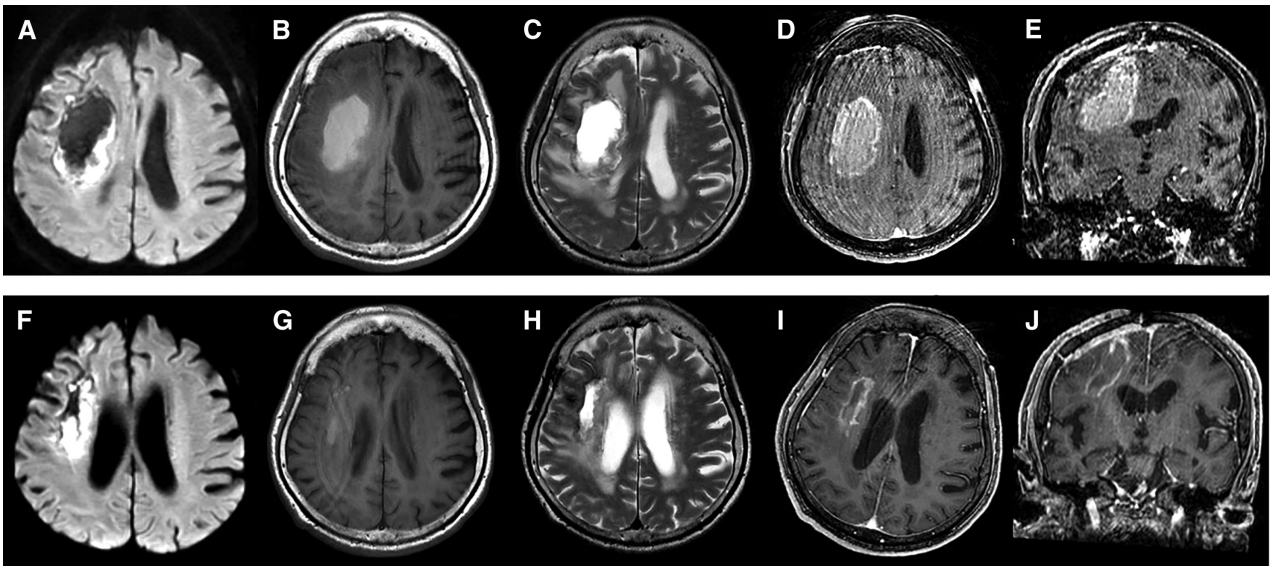

Fig. 4 (A–E) Brain MR imaging on postoperative day 16 demonstrating the cyst in the hematoma cavity. Diffusion-weighted image showing hyperintensity on the cyst wall (A). T1-weighted image showing hyperintensity (B). T2-weighted image showing hyperintensity (C). Cyst wall enhancement on axial (D) and coronal (E) MR images after gadolinium administration. (F–J) Brain MR imaging on postoperative day 33 demonstrating cyst shrinkage after steroid treatment. Diffusion-weighted image (F). T1-weighted image (G). T2-weighted image (H). Axial (I) and coronal (J) MR images after gadolinium administration. MR: magnetic resonance.

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.[25,26] 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. Serosanguinous 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.[25] 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.[26] 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.[27] 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.[25,26] 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 endothelial junction and reducing cerebrovascular permeability.[28] Given that thrombin induced BBB disruption 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.[18] Hematoma often expands during the first 6 hours after symptoms onset. Risk factors for hematoma expansion, including antiplatelet therapy, anticoagulant use, intervals from symptom onset to emergency arrival, hematoma volume, and spot sign, have been reported.[29] The effectiveness of minimally invasive hematoma evacuation has also been reported in recent years.[30] Brain edema around hematoma results in more severe and durable brain injury.[31] 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.[18] In the second phase (first 2 days), the coagulation cascade is activated, and thrombin induces edema formation and BBB disruption.[28] In the third phase (on about day 3), erythrocyte lysis results in the release of hemoglobin degradation products, including iron, into the extracellular space, contributing to delayed brain injury.[18,31]

Combination effect of thrombin and iron on BBB disruption

Thrombin can be neurotoxic, eliciting DNA fragmentation,[20] and can induce BBB disruption[21] and vasogenic edema.[22,23] Furthermore, the combination of iron and thrombin can augment its neurotoxic effect, leading to disruption of the BBB.[32,33] 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 erythrocyte lysis, including iron and gelatin–thrombin matrix use, may have contributed to BBB disruption and cyst formation.

Prevention of gelatin–thrombin matrix-related cyst

The gelatin–thrombin matrix demonstrates pseudoair hypoattenuation on brain CT within 48 hours after surgery.[34] Case 1 also exhibited pseudoair 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, particularly if the hematoma extends horizontally to the cortical surface. Furthermore, thrombin has concentration-dependent effects on the brain, and high concentrations induce brain damage.[19,24] 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.[17] 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 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 in cases where there are spaces blinded from view with the neurosurgical microscope.

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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