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ABSTRACT

BACKGROUND AND PURPOSE: Absorbable gelatin-thrombin matrix is increasingly being used in neurosurgical procedures; unlike other hemostats, the stable matrix is left undisturbed and fills the surgical bed after achieving hemostasis. We investigated the immediate postoperative radiographic imaging appearance of the gelatin-thrombin matrix in intracranial operative beds.

MATERIALS AND METHODS: Thirty-one consecutive patients (18 men, 13 women; mean age, 59 years) with 34 surgical cavities, had 31 brain MRIs and 9 head CTs performed ≤ 48 hours postoperatively. They were retrospectively reviewed. Images were evaluated independently by 2 neuroradiologists blinded to the surgical techniques. Surgical beds were evaluated for the presence of the gelatin-thrombin matrix, which appeared as pseudoair material (Hounsfield units ≤ −100) on CT, had characteristic T2-hypointense speckles in a T2-hyperintense background, and demonstrated complete gradient-recalled echo hypointensity on MR imaging. To determine the diagnostic performance of imaging features for the detection of the gelatin-thrombin matrix, the Fisher exact test for the association between imaging features and the presence of the gelatin-thrombin matrix and κ analysis for interobserver agreement were performed.

RESULTS: Hemostasis was achieved with standard methods in 12 surgical beds and with the gelatin-thrombin matrix in 22 beds. Interobserver agreement was substantial. The gelatin-thrombin matrix demonstrated pseudoair hypoattenuation (88% sensitivity, 100% specificity, 90% accuracy; $P = .067$, $\kappa = 0.74$) and distinctive T2-hypointense speckles in a background of T2-hyperintensity (81% sensitivity, 85% specificity, 82% accuracy; $P = < .001$, $\kappa = 0.76$). Combined characteristic T2 speckles and gradient-recalled echo hypointensity increased the specificity (81% sensitivity, 100% specificity, 88% accuracy; $P = < .001$).

CONCLUSIONS: The unique appearance (pseudoair on CT, T2 speckles with gradient-recalled echo hypointensity) of the gelatin-thrombin matrix should not be mistaken for gossypiboma, pneumocephalus, and/or hematoma.

ABBREVIATION: GRE = gradient-recalled echo

The achievement of hemostasis is of particular importance in neurosurgical procedures to ensure clear fields of vision for accurate surgical targeting and to prevent neurologic damage due to blood within the brain parenchyma. Pressure application, suture, and cautery have limited uses in brain surgery, with potential irreversible neurologic damage.[1] Bipolar coagulation at the bleeding site is effective in achieving hemostasis at the cost of longer operative times and wider surgical exposure. An armamentarium of hemostatic agents routinely used in neurosurgery includes cellulose-, gelatin-, and collagen-based agents; thrombin; and fibrin glue. They primarily stop bleeding by their contact activation of the clotting cascade and formation of an occlusive clot.[2] These agents effectively achieve hemostasis with various limitations. Fibrin glue requires a dry surface, obviating its use in an excessively oozing field. Gelatin Gelfoam (Pharmacia & Upjohn Company, Kalamazoo, Michigan) expands up to 320% with absorption of fluid and may compress the neural tissue.[3] Therefore, the necessary removal of Gelfoam from the surgical bed after achieving hemostasis risks rebleeding. Meticulous lining of the surgical bed with cellulose Surgicel (Ethicon, Somerville, New Jersey) is time-consuming and at times impossible through a narrow surgical corridor. Therefore, normal immediate postoperative surgical cavities contain extra-axial fluid and a small amount of independent air and hemostatic agents such as Surgicel along the wall.[4,5]

Gelatin-thrombin matrix (Floseal Hemostatic Matrix; Baxter

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From the Departments of Radiology (L.J.B., I.Z.H., K.O.L., S.M., S.W.) and Neurosurgery (J.Y.L.), University of Pennsylvania Health System, Perelman School of Medicine, Philadelphia, Pennsylvania; and Department of Radiology (I.Z.H.), Pennsylvania Hospital, Philadelphia, Pennsylvania.

Please address correspondence to Kim O. Learned, MD, Department of Radiology-Neuroradiology Division, University of Pennsylvania Health System, University of Pennsylvania Perelman School of Medicine, Hospital of the University of Pennsylvania, 219 Dulles Bldg, 3400 Spruce St, Philadelphia, PA 19104; e-mail: Kim.Learned@uphs.upenn.edu

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Healthcare, Deerfield, Illinois) is an absorbable bovine gelatin–human thrombin composite. Following the approval of Floseal in neurosurgery in 2001 by the US Food and Drug Administration based on the safety and efficacy data from a multicenter prospective randomized clinical trial, it has been increasingly used in spine, brain, pituitary, and endoscopic sinus surgeries.[6-9] The prospective study of 214 patients undergoing cranial and spinal surgeries demonstrated the efficacy and safety of Floseal in controlling operative bleeding and minimizing damage to the surrounding healthy nervous tissue while reducing operative time.[7] Additionally, it was shown to be effective in coagulopathic disorders and refractory bleeding.[7] The advantages include fast preparation, easy delivery with a syringe applicator to various surgical beds, a hydrophilic matrix allowing effective adherence to a wet surgical field, and a granular gelatin matrix conforming to any irregular surgical cavity.[6] The granular gelatin particles swell maximally 10%–20% and are left in the surgical bed, providing a gentle tamponade effect and stable clot for effective hemostasis.[3,7,8,10] The unique postoperative radiographic imaging appearance of Floseal has been scarcely described and can be mistaken for gossypiboma, hematoma, and/or pneumocephalus. We investigated the immediate postoperative CT and MR imaging appearances of the gelatin-thrombin matrix in intracranial operative beds.

MATERIALS AND METHODS

Patients

We retrospectively reviewed our CNS tumor data base from September 2011 to June 2013 to identify patients who underwent surgical resection of intracranial neoplasms. Inclusion criteria were the following: 1) newly diagnosed neoplasms, 2) ≥95% gross total resection, 3) postoperative head CT and/or brain MR imaging performed within 48 hours after surgeries, and 4) mean size of the surgical cavities of ≥1 cm. Exclusion criteria were the following: 1) previously resected or irradiated neoplasms, pituitary or skull base neoplasms; 2) surgical biopsy; 3) mean size of surgical cavities of <1 cm; and 4) a nondiagnostic examination. Thirty-one consecutive patients (18 men, 13 women; mean age, 59 years) met the selection criteria. Thirty-four surgical cavities were evaluated with 31 brain MRIs and 10 head CTs. The resected neoplasms were glioblastoma ($n = 6$), hemangioblastoma ($n = 1$), metastasis ($n = 18$), meningioma ($n = 4$), and vestibular schwannoma ($n = 2$).

Imaging Methods and Analysis

Brain MRI was performed on 1.5T systems (Signa HD, Optima; GE Healthcare, Milwaukee, Wisconsin) with the following parameters of the sequences used for the imaging analysis: axial T2 FSE (TR/TE, 3000–4000/100–130 ms; thickness, 5 mm; skip, 1 mm), axial gradient-recalled echo (GRE) (TR/TE, 700/20 ms; thickness, 5 mm; skip, 1 mm), and axial unenhanced and enhanced T1 spin-echo (TR/TE, 500–400/9.5–12 ms; thickness, 5 mm; skip, 1 mm). Patients received 0.1 mmol/kg of gadolinium intravenously (MultiHance; Bracco Diagnostics, Princeton, New Jersey). Unenhanced head CT was performed in the helical mode (1.25-mm thickness, 120 kV, 250 mA; Somatom Definition Flash, Siemens, Erlangen, Germany) and was reconstructed in 5-mm axial images.

Two neuroradiologists blinded to the surgical technique independently reviewed the images and recorded the dominant imaging features seen in ≥75% volume of the surgical bed. Discrepancies between readers were resolved by consensus adjudication. The head CT was evaluated in brain and lung windows (approximate window widths of 150 and 1500, respectively) for the presence of pseudoair material (marked hypoattenuation ≤ −100) or other findings including air, CSF fluid, and hyperattenuated acute blood. The internal architecture and signal intensity of surgical beds were assessed with MR imaging. On the T2WI, the surgical bed was evaluated for the presence of the characteristic T2-hypointense speckles in the T2-hyperintense background of the gelatin-thrombin matrix versus other findings including T2-hyperintensity similar to that in CSF, T2-isointensity to brain, T2-hypointensity, or heterogeneous signal intensity. On the GRE sequence, the characteristic speckles on T2WI were correlated for the presence of complete hypointensity that was not secondary to susceptibility effects from pneumocephalus, calvaria, skull base, or metallic surgical hardware. Whereas hypointensity along the surgical margin and/or randomly distributed in the cavity was categorized as partial hypointensity on GRE, T1WI was assessed for the presence of T1-hyperintensity and enhancement. The imaging findings were correlated with the operative notes.

Statistical Analysis

Inter-rater agreement was measured for each imaging feature by using the κ statistic to determine consistency among the readers. Interpretation of the κ values followed the proposed standards of Landis and Koch: 0–.20 (slight), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1.00 (almost perfect).[11] The diagnostic performances of the imaging features, including sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, were evaluated by using a 2×2 contingency table. A Fisher exact test was used to examine the association between the imaging features with the surgical use of the gelatin-thrombin matrix; a P value $< .05$ was considered significant. Statistical analysis was performed by using the Statistical Package for the Social Sciences, Version 20.0 (IBM, Armonk, New York).

RESULTS

In 12 surgical beds (mean diameter, 2.49 ± 0.63 cm), hemostasis was achieved with standard methods, including warm water irrigation; bipolar cautery; and application of Surgicel, Gelfoam, and/or collagen sponge. In 22 surgical beds (mean diameter, 2.49 ± 0.65 cm), only Floseal was used to achieve hemostasis, especially in cases of coagulopathy and/or excessive bleeding or when the standard techniques were deemed inappropriately time-consuming, thereby unfavorably prolonging the operative time, or technically difficult with potential injury to the surrounding healthy tissue (Figs 1 and 2).

The gelatin-thrombin matrix in the surgical bed appeared as a space-occupying material with pseudoair hypoattenuation on CT (−1000 ≤ Hounsfield units, ≤ −100), distinctive T2-hypointense speckles on a T2-hyperintense background, and complete hypointensity on GRE with high specificity (Figs 1 and 2). The diagnostic performances of these imaging features for the presence of the gelatin-thrombin matrix in the surgical bed are summarized in the Table. The complete hypointensity on GRE of the speckles seen on T2WI increased MR imaging diagnostic confi-

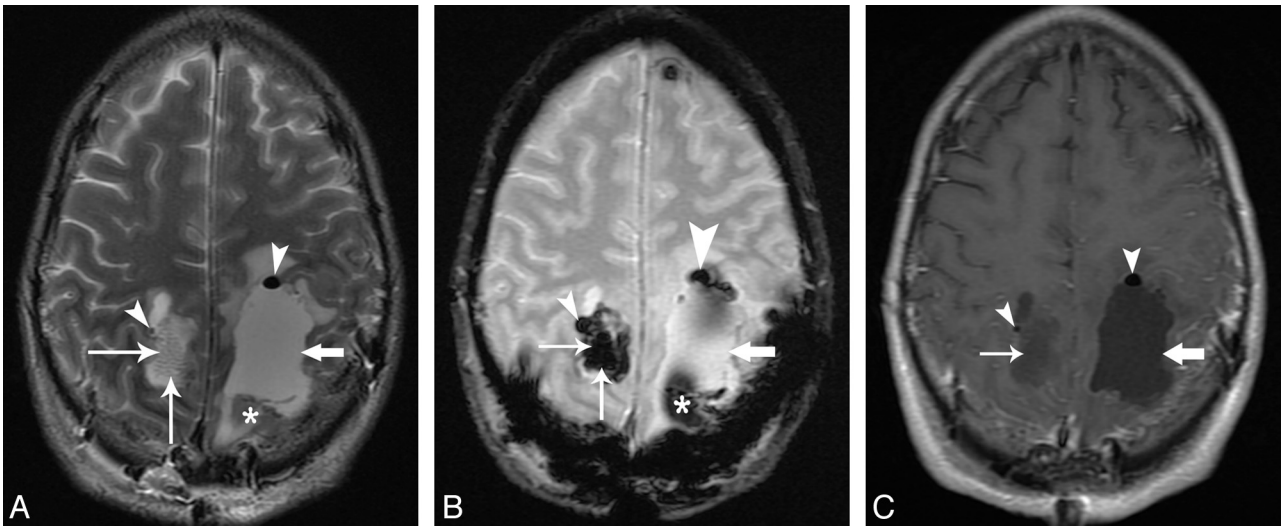

FIG 1. A 27-year-old man who has sequential resection of 2 brain metastases. Hemostasis of the first resection bed in the left parietal lobe is achieved with the standard technique. The gelatin-thrombin matrix is used in the subsequent second resection bed in the right parietal lobe to decrease operative time and effectively control bleeding from hypervascular sarcoma metastasis. *A*, Axial T2WI demonstrates the left parietal bed (*thick arrow*) filled with CSF containing a small amount of blood products posteriorly (*asterisk*) and the right parietal bed filled with a distinctive organized cluster of T2-hypointense speckles (*thin arrows*) almost in stacked layers in the T2-hyperintense background, characteristic of the gelatin-thrombin matrix. *B*, Axial GRE image demonstrates the corresponding complete hypointensity of the gelatin-thrombin matrix (*thin arrows*) filling the right cavity, different from the focal susceptibility of blood products (*asterisk*) in the left cavity. *C*, Axial T1WI shows CSF signal in the left cavity and isointensity in the right cavity without enhancement. Scattered bubbles of air (*arrowheads*) are present in the nondependent portion of the surgical beds with susceptibility on GRE.

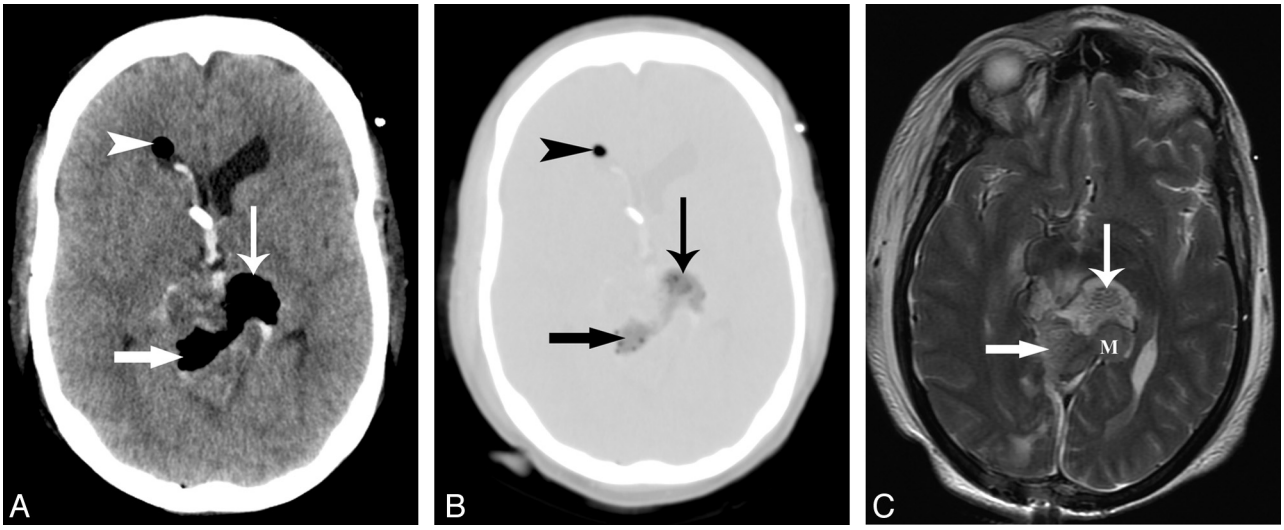

FIG 2. A 48-year-old woman who has a resection of a 5-cm pineal region meningioma. *A* and *B*, Axial CT images of the pineal resection bed in brain and lung windows, respectively, demonstrate the characteristic pseudoair hypoattenuation of the gelatin-thrombin matrix (*thin and thick arrows*), which can be easily mistaken for pneumocephalus. *C*, Axial T2WI illustrates characteristic T2-hypointense speckles of the gelatin-thrombin matrix (*thin arrow*) in the background of T2-hyperintensity. Note the less distinct speckles in the background of T2-isointensity (*thick arrow*), which may result in a falsenegative for the detection of the gelatin-thrombin matrix on MR imaging if CT is not available for correlation. Residual T2-isointense meningioma (M) shows avid enhancement on postcontrast T1WI (T1WI not shown).

dence in identifying the gelatin-thrombin matrix with a sensitivity of 81% and a specificity of 100% ($P < .001$). The presence of all 3 CT and MR imaging features had a high specificity of 100%, with an acceptable sensitivity of 75% and an accuracy of 80% for detecting the gelatin-thrombin matrix in the postoperative bed.

All the gelatin-thrombin matrix–containing cavities demonstrated a T1-isointense center. Even though 13 of 22 cavities had no T1-hyperintense rim and 9 cavities had a variable degree of peripheral T1-hyperintense rim, these findings were not statistically significant ($P = .157$). None showed enhancement.

The interobserver reliability for the raters was substantial for identifying the characteristic T2-hypointense speckles ($\kappa = 0.76$)

Diagnostic performances of different imaging features for the detection of gelatin-thrombin matrix

Imaging Sequence	Sensitivity	Specificity	Accuracy	*P* Value
T2	0.81	0.85	0.82	<.001
GRE	1	0.92	0.97	<.001
T2+GRE	0.81	1	0.88	<.001
CT	0.88	1	0.90	.067
CT+MRI	0.75	1	0.80	.133

and pseudoair hypoattenuation ($\kappa = 0.74$) and excellent for identifying the corresponding complete GRE hypointensity of gelatin-thrombin matrix ($\kappa = 1$).

DISCUSSION

Gelatin-Thrombin Matrix Application in Cranial Surgery

Floseal consists of a bovine-derived gelatin matrix component and a human-derived thrombin component.[1,2,7,10] The gelatin-thrombin matrix is readily available for delivery to the surgical bed by mixing the gelatin granules with a reconstituted thrombin solution in a syringe. Hemostasis of the deepest portion of the surgical cavity is achieved by back-filling of the gelatin-thrombin matrix by using a syringe applicator that effortlessly passes through the narrow surgical corridor (Fig 2). The unique characteristic of Floseal is the requirement for the presence of blood at its application site for activation. The hydrophilic matrix adheres well to wet tissue, and the gelatin granules conform to the irregular geometry of the bleeding site. The material swells maximally 10%–20% within 10 minutes of contact with blood or fluids, providing a gentle tamponade effect and a mechanically stable matrix for clot formation.[3,7,10] Direct application of the gelatin-thrombin matrix on an actively oozing or spurting bleeding site exposes the patient's blood to a matrix of highly concentrated thrombin, accelerating clot formation by a combination of rapid conversion of the patient's fibrinogen to fibrin and contact activation of platelets. After achieving hemostasis, only the excess matrix not incorporated into the clot is gently irrigated out of the surgical bed; thus, the stable matrix-clot integration is left undisturbed.[10] The median times to cessation of bleeding were shorter than those achieved with other hemostatic agents with a higher hemostasis success rate of 96%.[6] Therefore, Floseal has been increasingly used, and its safety and efficacy for achieving hemostasis in spine, brain, pituitary, and endoscopic sinus surgeries have been widely published in the surgical literature.[6-9]

Immediate Postoperative Head CT and Brain MR Imaging

The immediate postoperative surgical cavities normally contain extra-axial fluid and a small amount of nondependent air (Fig 1).[4] Spiller et al[5] demonstrated that Surgicel-induced clots contained methemoglobin, resulting in a T1-hyperintense rim along the cavity lined by Surgicel on early postoperative MR imaging, not to be confused with enhancing residual tumor. In our cohort, all gelatin-thrombin matrix–containing cavities had central T1-isointensity, probably reflecting the acute clot incorporated in the matrix. Even though a majority (59%) of gelatin-thrombin matrix cavities in our study lacked the T1-hyperintense rim, the finding did not reach the statistical significance needed to distinguish Floseal- from Surgicel-lined cavities.

The gelatin granules in Floseal derived from bovine dermis swell on contact with fluid and entrap microbubbles in the matrix, mimicking air and fat with Hounsfield unit ≤ -100 on postoperative CT. This finding is similar to reported marked hypoattenuation of the surgically placed gelatin sponge used in abdominal surgery (Fig 2).[12,13] The gelatin-thrombin matrix incorporates the gelatin granules into the clot, rather than providing a surface for trapping the clot as seen with the gelatin sponge. As a result, the gelatin-thrombin matrix is ball-like, which is different from the linear arrangement of the gelatin sponge or the focal linear gas collection of Surgicel.[13] These trapped microbubbles and the stable integration of the cross-linked gelatin granule platform and fibrin clot likely account for the organized cluster of T2-hypointense speckles in the surgical cavity. Most interesting, 72% of these Floseal clusters had a unique appearance on axial T2WI of particles in stacked layers. In addition, organized fluid absorbed by the granules and retained in the matrix contributes to the T2-hyperintense background (Figs 1 and 2). These microbubbles and clot formation in the matrix cause magnetic field inhomogeneity with T2* effects evident by blooming susceptibility on GRE of the gelatin-thrombin matrix in the surgical cavity.

The characteristic T2-hypointense speckles in a background of T2-hyperintensity had a moderate sensitivity of 81% and a specificity of 85% for the detection of the gelatin-thrombin matrix ($P < .001$). The proportions of absorbed fluid and blood in the gelatin-thrombin matrix and clot formation all contribute to the signal intensity and internal architecture of Floseal in the surgical bed. Consequently, the surgical beds containing Floseal may have variable T2 signal intensity, which may obscure visualization of the characteristic speckles on T2WI. In our cohort, the false-negative for the presence of Floseal in the surgical bed had T2-isointensity, which probably resulted from absorption of more blood products than fluid in the matrix. Even though these falsenegative cases demonstrated complete hypointensity on GRE, suggestive of the gelatin-thrombin matrix with the highest diagnostic accuracy in our cohort, a variety of reasons accounting for susceptibility in the postoperative bed in routine clinical practice precludes sole use of the GRE sequence hypointensity as an indicator of the presence of the gelatin-thrombin matrix. Likewise, the false-positive T2-hypointense speckles demonstrated heterogeneous hypointensity on GRE of blood products rather than the gelatin-thrombin matrix. For these reasons, these pitfalls can be avoided by combining findings of both T2-speckles and corresponding GRE complete hypointensity to identify the gelatin-thrombin matrix with a high specificity of 100% and 88% accuracy. Furthermore, the inter-rater discrepancy, false-negative, and false-positive findings occurred in irregular-geometry surgical beds and small cavities, which affected visibility and assessment of their internal architecture.

Retained surgical sponge after craniotomies has been described as a hyperattenuated serpiginous structure on CT and a hypointense serpentine foreign body with susceptibility effects on the gradient-echo sequences on MR imaging.[14] The susceptibility on the GRE sequence of the organized thrombin clot in the gelatin-thrombin matrix and its unique internal architecture create a pseudomass, which should not be mistaken for an unintended retained foreign body or a gossypiboma during immediate postoperative imaging.

Limitations

We excluded the pituitary and skull base lesions and small surgical cavities along the calvaria and skull base to eliminate the confounding factor of bone and air susceptibility effects and to optimize visual assessment of the surgical cavity. Exclusion of prior surgery and radiation, subtotal resection, and biopsy cases in our cohort minimized the complexity of the evaluated surgical beds and eliminated variables that may affect our ability to evaluate the gelatin-thrombin matrix accurately. Consequently, the findings of our cohort may not be applicable to all patient populations. A combination of excluding

small surgical cavities from our analysis and preferential use of Floseal in sizable surgical beds to decrease the operative time by our surgeons caused a selection bias with 65% of the surgical cavities containing the gelatin-thrombin matrix in our imaging analysis. The Floseal and standard-hemostasis groups were age-matched and had a similar average surgical cavity size of 2.49 cm.

Our random Hounsfield unit measurements of the pseudoair gelatin-thrombin matrix ranged from −190 to −110. Given the irregular geometry of most surgical beds and likely variable swelling and fluid absorption of the gelatin matrix, an absolute Hounsfield unit measurement cutoff as a determination for the presence of the gelatin-thrombin matrix is impractical in clinical practice. Furthermore, simple visualization of the pseudoair of the surgical bed on a wide window setting in our cohort had a high specificity of 100% and accuracy of 90% for depicting the presence of the gelatin-thrombin matrix, even though the finding did not reach statistical significance due to small sample size. Following tumor resection, postoperative brain MR imaging is necessary for baseline evaluation of the resection result and unexpected postoperative complications. Therefore, head CT is performed as adjunctive imaging in patients with a concerning postoperative course, explaining our small number of postoperative CT scans.

Standard instructions for use of Floseal in brain surgery are assumed to offset the limitation of operator-dependent results and the postoperative imaging findings thereof. However, the removal of any excess Floseal that is not incorporated into the hemostatic clot can vary among patients, surgical beds, and surgeons. Therefore, close communication with the surgeon is paramount for clinically meaningful assessment of the postoperative bed.

Future Research

Accurate assessment of the postoperative cavity after brain tumor resection is critical in neoplastic surveillance. The studies in rat brains demonstrated that Floseal is biocompatible and resorbed within 6–8 weeks, though it elicits granulomatous inflammatory reactions for up to 28 days.[3,15] There are case reports on the inflammatory reaction, granuloma, and calcification formation in response to Floseal in the body, mimicking tumor.[16,17] To the best of our knowledge, there has not been a clinical report on the length of normal resorption of surgically implanted intracranial gelatin-thrombin matrix. The blood-brain barrier effectively shields the intraparenchymal brain from the usual inflammatory processes seen outside the brain; thus, the normal degradation pathways that may resorb surgically implanted foreign bodies in the rest of the body may not accurately reflect the intracranial situation. Hemostat-associated gossypiboma can mimic recurrent intracranial neoplasm.[18] Hence, imaging can serve as the least invasive method for following the pathway of healing, and imaging study of normal gelatin-thrombin matrix resorption is imperative to avoid mistaking the matrix for neoplasm, hematoma, and/or abscess.

CONCLUSIONS

The gelatin-thrombin matrix Floseal has distinctive pseudoair hypoattenuation on CT and T2-hypointense speckles in a background of the T2-hyperintense surgical bed on MR imaging during the immediate postoperative period. Its unique space-occupying appearance should not be mistaken for retained surgical sponge, which is a serpiginous structure with CT-hyperattenuation, T2-hypointensity, and GRE-susceptibility; pneumocephalus; and/or hematoma.

Disclosures: Linda J. Bagley—*RELATED: Support for Travel to Meetings for the Study or Other Purposes*: University of Pennsylvania, *Comments*: reimbursement for travel expenses to the American Society of Neuroradiology meeting in San Diego, where this was a poster presentation, *UNRELATED*: Pfizer Pharmaceuticals, *Comments*: reviewer in an osteoporosis drug trial, *Payment for Lectures (including service on Speakers Bureaus)*: International Diagnostics Course Davos, Davos, Switzerland, *Comments*: honorarium for participation in neuroradiology review course. John Y.K. Lee—*RELATED*: *Other*: speaker for Baxter (maker of Floseal), *UNRELATED*: Storz,* *Comments*: research grant, endoscopy company, *Stock/Stock Options*: Visionsense,* *Comments*: 3D endoscopy company. *Money paid to the institution.

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