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Case report

Repeated short-term recurrence of a chronic subdural hematoma associated with metastasis to hematoma capsule originating from extracranial malignant tumor

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Key words: chronic subdural hematoma, hematoma capsule, recurrence, tumor, metastasis

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Abbreviation list:

CSDH = chronic subdural hematoma

CT = computed tomography

MMA = middle meningeal artery

MRI = magnetic resonance imaging

NBCA = n-butyl-2-cyanoacrylate

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ABSTRACT

Background: The recurrence rate of chronic subdural hematoma (CSDH) after trepanation is relatively high, and involves various factors. We encountered an extremely rare case in which metastasis of an extracranial malignant tumor to the hematoma capsule was thought to be causing short-term repeated recurrences of CSDH.

Case Description: The patient was a 74-year-old man who had undergone burr-hole evacuation of left CSDH 7 months earlier and had been receiving chemotherapy for stage IV gastric cancer for the preceding 6 months. He presented with symptoms of right hemiparesis and was diagnosed with left CSDH. Burr-hole evacuation was performed twice, but the hematoma enlarged again both times within a short period. A third burr-hole evacuation was performed after middle meningeal artery embolization, but the hematoma again enlarged shortly thereafter. Hematoma enlargement was finally suppressed by extracting the hematoma capsule under craniotomy. In histopathological examinations, hematoxylin and eosin staining showed poorly differentiated adenocarcinoma primarily along the luminal side of the hematoma capsule, and immunohistochemical staining showed results identical to findings from the existing gastric cancer. Pathological results confirmed metastasis of the gastric cancer to the hematoma capsule, and this was considered to be the cause of short-term repeated recurrence of CSDH.

Conclusions: To the best of our knowledge, this is the first report of metastasis to a hematoma capsule originating from an extracranial malignant tumor. The clinical course in the present case suggests metastasis of extracranial malignant tumor to the CSDH capsule as an extremely rare cause of recurrence.

INTRODUCTION

Although burr-hole evacuation is an established standard method for treating chronic subdural hematoma (CSDH), the postoperative recurrence rate is relatively high, at 8-33%.¹⁻¹² Factors associated with recurrent CSDH include male sex, old age, habitual consumption of alcohol, diabetes, liver dysfunction, cerebral atrophy, use of antithrombotic agent, hemodialysis, coagulopathy, condition after cerebrospinal fluid shunting, and presence of malignant tumor.^{1, 9-14} Some reports have described recurrent CSDH associated with dural metastasis of malignancy.¹⁵⁻¹⁷ However, metastasis of a malignant tumor to the hematoma capsule does not appear to have been reported as a cause of recurrence. We provide herein the first description of a case of CSDH showing repeated recurrence within a short amount of time and attributed to metastasis of gastric cancer to the CSDH capsule.

CASE REPORT

History and Examination

The patient was a 74-year-old man who had undergone burr-hole evacuation of left CSDH at another hospital 7 months earlier. Computed tomography (CT) of the head performed 4 days after that surgery revealed no recurrence, and head examinations had not been performed since then. Advanced gastric adenocarcinoma (stage IV) had been identified 6 months earlier, based on high levels of tumor markers, and chemotherapy was started in our hospital using capecitabine (Xeloda[®]; Hoffmann-LaRoche, Nutley, NJ). The patient had not been taking any antiplatelet drugs or anticoagulants and did not habitually consume alcohol. The present illness started with a fall due to right hemiparesis and subsequent visit to our hospital. Head CT revealed left CSDH, and the hematoma showed homogeneous hypodensity with no septa (**Fig. 1A**). Blood test results indicated pancytopenia (leukocytes, 5420/ μ L; erythrocytes, 2,840,000/ μ L; hemoglobin, 9.1 g/dL; platelets, 119,000/ μ L), which was attributed to the

myelosuppressive effects of anti-cancer drugs. In terms of the coagulation system, normal results were observed for prothrombin time (11.3 s; prothrombin time-international normalized ratio, 0.98), activated partial thromboplastin time (24.3 s), fibrinogen (386 mg/dL), D-dimer (1.5 $\mu\text{g/mL}$), and fibrin degradation products (3.8 $\mu\text{g/mL}$). Protein C (137%), protein S (78%), and antithrombin III (106%) were almost within the normal range (**Table 1**). No other abnormalities were observed from blood biochemistry.

Operative course

Burr-hole irrigation and drainage were performed on Day 1 of hospitalization (**Fig. 1E**). However, head CT performed 5 days after the first surgery (Day 6) showed that the volume of hematoma had reverted to the preoperative level (**Fig. 1B**), and burr-hole irrigation and drainage were again performed (**Fig. 1F**). At the same time, oral goreisan at 7.5 g/day and ibudilast at 30 mg/day were administered to prevent recurrence. However, head CT performed 6 days after this second surgery (Day 12) showed that the hematoma volume had reverted to the preoperative level (**Fig. 1C**). Refractory CSDH was therefore indicated, and embolization of the left middle meningeal artery (MMA) was planned. Contrast-enhanced magnetic resonance imaging (MRI) of the head performed on Day 13 showed uniform contrast enhancement of the hematoma capsule, and the antero-posterior and cranio-caudal ends of the hematoma capsule in particular showed partial thickening (**Fig. 2**). No metastases to the intracranial sites other than the hematoma capsule were observed. Pancytopenia had improved on blood testing due to temporary discontinuation of anti-cancer drugs, and no bleeding tendencies were observed on physical examination. Left MMA embolization under local anesthesia was performed on Day 15. After placing a 5-Fr guiding catheter into the origin of the left external carotid artery, the microcatheter was advanced as distally as possible into the MMA to perform super-selective angiography, revealing abnormal vascular

networks with an extremely rich blood flow not only at the outer membrane but also at the inner membrane of the hematoma (**Fig. 3A, B**). These abnormal vascular networks were occluded by injecting 20% n-butyl-2-cyanoacrylate (NBCA). External carotid artery imaging after embolization showed occlusion of the MMA and disappearance of the distal MMA-derived abnormal vascular networks (**Fig. 3C, D**). Burr-hole irrigation and drainage were performed following embolization, and satisfactory MMA embolization was considered to have been achieved, since postoperative CT of the head showed an NBCA cast at the inner membrane of the hematoma (**Fig. 1G**). However, head CT performed 6 days after the third surgery (Day 21) showed that the amount of hematoma had once again reverted to the preoperative state (**Fig. 1D**). As radical treatment, extraction of the hematoma capsule was considered necessary, and left craniotomy was therefore performed under general anesthesia on Day 35. The hematoma capsule was partially thickened and adhesion of the hematoma capsule to the arachnoid mater and dura mater was quite mild, with no marked thickening. The hematoma capsule was almost completely extracted. Findings suggestive of dural metastasis were absent, and the procedure was concluded upon closure of the dura mater.

Pathological findings

Macroscopic examination of the surgically extracted hematoma capsule revealed partial thickening and predominant organization (**Fig. 4**). Hematoxylin and eosin staining showed poorly differentiated adenocarcinoma with tendencies of eccentric nuclei and duct formation primarily along the luminal side of the hematoma capsule (**Fig. 5A, B**). Immunohistochemical staining showed locally positive results for CDX2, negative results for CK7, and positive results for CK20, strongly resembling findings for the existing gastric cancer (**Fig. 5C-E**). Cell morphology and immunohistochemical staining confirmed metastasis from the gastric cancer to the hematoma capsule. However, pathological

examinations of the dura mater and hematoma in the capsule cavity were not performed.

Postoperative course

Postoperative CT of the head showed that the hematoma capsule had been extracted and revealed NBCA cast in the dura mater (**Fig. 1H**). Transient partial spasm on the right side of the mouth and cheek was observed, but was able to be controlled with anticonvulsive agents. CT and MRI examinations did not reveal any recurrent enlargement of the left subdural hematoma. No neurological abnormalities were observed, and the patient was discharged to home on Day 59.

DISCUSSION

An association between CSDH recurrence and history or presence of malignant tumor has been reported.^{14, 18} The mechanisms underlying recurrent CSDH in the presence of malignancy are postulated to be as follows: patients with malignant tumor show elevated levels of circulating cytokines such as interleukin-6, vascular endothelial growth factor, and basic fibroblast growth factor, which result in activation of the phosphoinositide 3 kinase/Akt pathway at the outer membrane of the hematoma, and subsequent enlargement of the hematoma.¹⁴

In the present case, no cause of CSDH recurrence aside from malignant tumor could be detected, and the presence of malignant tumor was thought to be involved in CSDH recurrence. We therefore performed contrast-enhanced MRI of the head after the second recurrence of CSDH, to investigate any involvement of the malignant tumor, but no abnormalities other than thickening and contrast enhancement of the hematoma capsule were identified. However, pathological examinations revealed metastasis of gastric adenocarcinoma to the hematoma capsule, suggested to represent the cause of repeated

short-term recurrence of CSDH. CSDH recurrence by metastasis of malignant tumor to the hematoma capsule is thought to occur via similar mechanisms to induction of subdural hematoma through dural metastasis of malignant tumors. Such mechanisms include rupture of the fragile tumor neovessels, extravascular leakage of fluid due to hyperpermeability of the premature neovessels, extravascular leakage of fluid caused by elevated hydrostatic pressure due to tumor cells blocking blood outflow pathways from the hematoma capsule, and mucin production by adenocarcinoma.^{16, 17, 19} The hematoma in the present case appeared hypodense on CT at the time of CSDH recurrence (**Fig. 1B-D**), indicating that there may have been more fluid than blood cells in the cavity of the hematoma capsule.

The present case showed weak evidence of meningeal dissemination based on clinical symptoms and head MRI, indicating that metastasis to the hematoma capsule was unlikely to have been caused by meningeal dissemination. The patient in the present case had undergone burr-hole evacuation to treat left CSDH 7 months earlier, and follow-up was only conducted up to 4 days postoperatively. Giant capillaries are known to be present between the MMA and outer membrane of the hematoma,^{20, 21} and we therefore deduced that hematogenous metastasis of the extracranial gastric cancer to the outer membrane of the hematoma had occurred prior to this presentation. Only two reports have described pathological findings confirming invasion of malignant cells to the subdural membrane or subdural hematoma associated with dural metastasis.^{17, 19} However, metastasis to the hematoma capsule originating from an extracranial malignancy does not appear to have been reported. Although pathological examinations of the dura mater were not performed in this case, invasion of malignant cells to the hematoma capsule associated with dural metastasis was unlikely to have occurred, because findings suggestive of dural metastasis were absent during the surgeries. Although pathological examinations of the hematoma in capsule cavity also had not been performed in this case, poorly differentiated adenocarcinoma was evident along the

cavity of the hematoma capsule, and tumor cells were most likely present in the hematoma. If pathological examination of the hematoma had been performed at the time of trepanation, then the association with gastric cancer might have been detected earlier.

CONCLUSIONS

The clinical course in the present case suggests that metastasis of an extracranial malignant tumor to the CSDH capsule represents a potential, albeit extremely rare, cause of CSDH recurrence. When metastasis of a malignant tumor to the hematoma capsule is suspected, suppression of CSDH enlargement may be difficult unless the hematoma capsule is extracted via craniotomy.

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Conflict of interest statement

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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FIGURE LEGENDS

Fig. 1. Findings for CT of the head before and the day after each of the four surgeries.

Before (A) and after (E) the first burr-hole evacuation, before (B) and after (F) the second burr-hole evacuation, before (C) and after (G) the third burr-hole evacuation and MMA embolization, and before (D) and after (H) hematoma capsule extraction under craniotomy. With NBCA embolization of the MMA, the NBCA cast is apparent within the inner membrane of the hematoma (arrowheads) and dura mater (arrows).

Fig. 2. Axial (left) and coronal (right) views on contrast-enhanced MRI of the head.

Uniform contrast enhancement of the hematoma capsule is observed, and the antero-posterior and cranio-caudal ends of the hematoma capsule, in particular, show partial thickening. No metastases to brain parenchyma or meninges, leakage of contrast agent, or presence of septa in the hematoma cavity are observed.

Fig. 3. Super-selective angiography of the MMA (A, antero-posterior; B, lateral) and external carotid artery angiography after MMA embolization (C, antero-posterior; D, lateral)

A, B) Super-selective angiography of the MMA shows abnormal vascular networks with rich blood flow not only in the outer membrane of the hematoma (arrowheads), but also in the inner membrane of the hematoma (arrows). C, D) External carotid artery angiography after MMA embolization with 20% NBCA shows occlusion of the MMA and disappearance of the distal MMA-derived abnormal vascular networks.

Fig. 4. Macroscopic examination of the hematoma capsule.

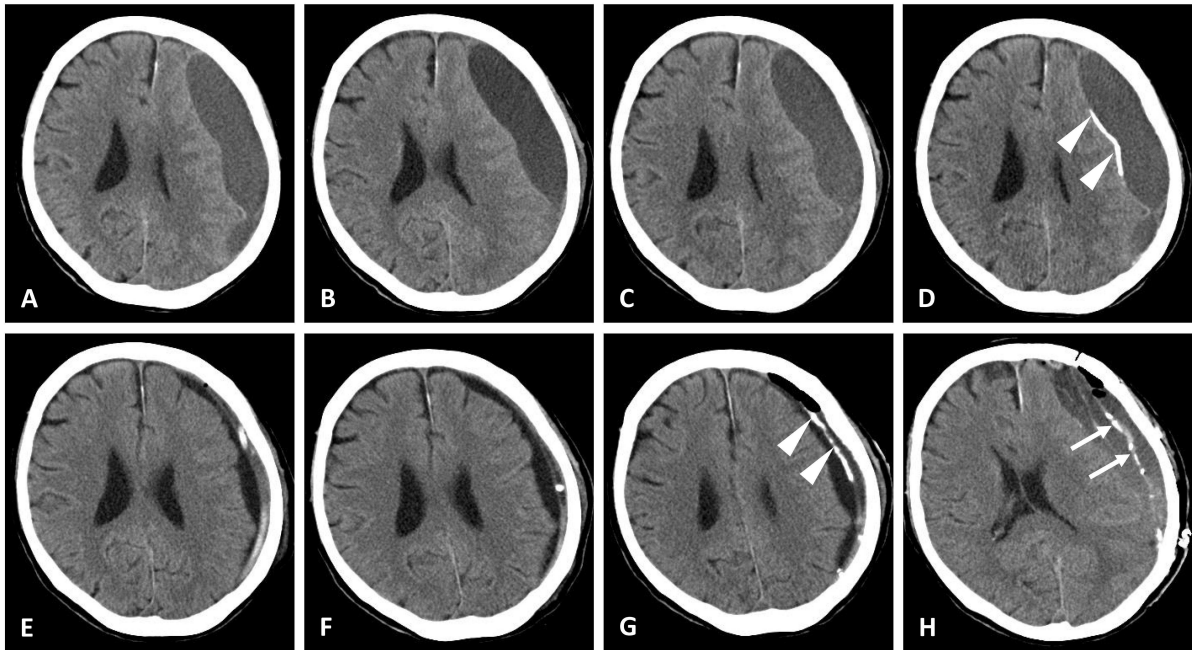
Macroscopic examination shows partial thickening and predominant organization of the hematoma capsule. Scale bar indicates 30 mm.

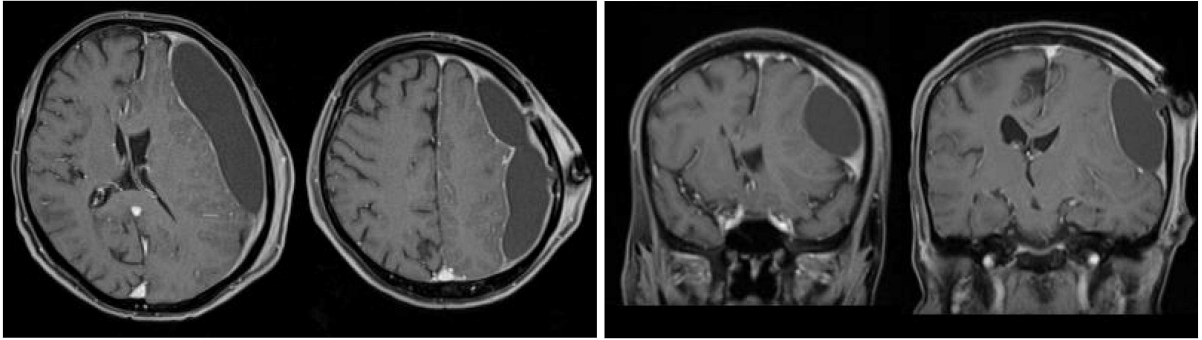
Fig. 5. Pathological findings of the hematoma capsule.

A) Hematoxylin and eosin staining shows poorly differentiated adenocarcinoma with tendencies of eccentric nuclei and duct formation primarily along the luminal side of the hematoma capsule. Scale bar in A indicates 1 mm. B) Hematoxylin and eosin staining of the magnified rectangular area in Figure 5A. C-E) Immunohistochemical staining of the magnified rectangular area in Figure 5A; CDX2 is locally positive (C), CK7 is negative (D), and CK20 is positive (E), indicating the same results as the existing gastric cancer. Cell morphology and immunohistochemical staining confirm metastasis of the existing gastric cancer to the hematoma capsule. Arrows in A-E point to the direction of the luminal side of the hematoma capsule. Scale bars in B-E indicate 200 μm .

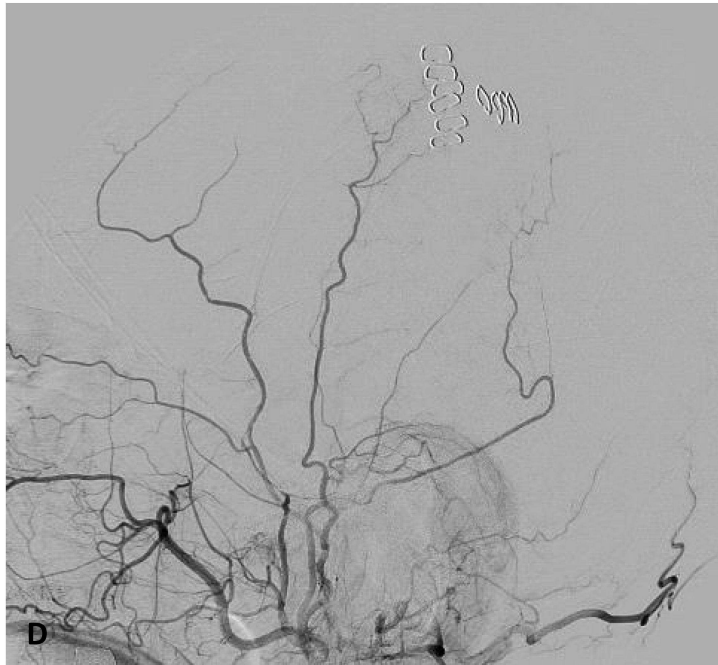
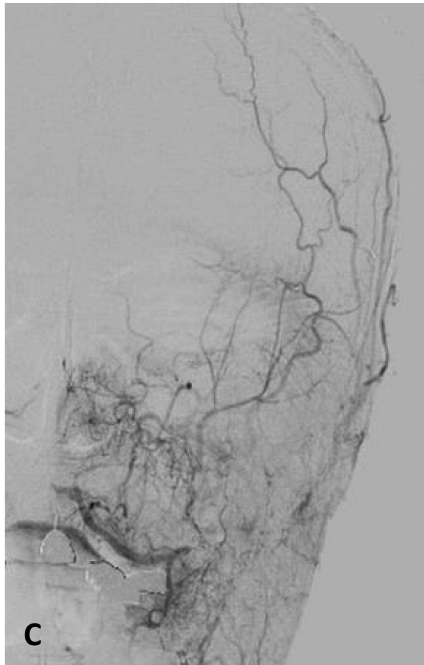
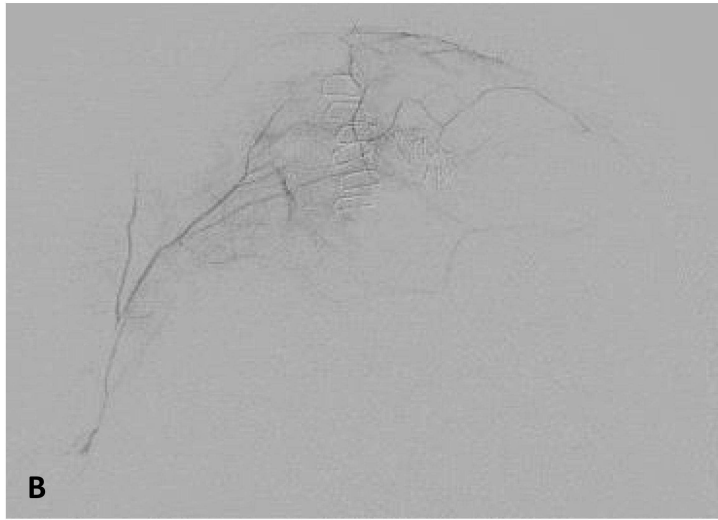
Table 1. Blood tests related to coagulation system

Blood tests	Measured values	Normal range
Prothrombin time (seconds)	11.3	10–15
Prothrombin time-international normalized ratio	0.98	0.86–1.14
Activated partial thromboplastin time (seconds)	24.3	24–39
Fibrinogen (mg/dL)	386	200–400
D-dimer ($\mu\text{g/mL}$)	1.5	0.0–1.0
Fibrin degradation products ($\mu\text{g/mL}$)	3.8	0.0–5.0
Protein C (%)	137	64–146
Protein S (%)	78	67–164
Antithrombin III (%)	106	70–130





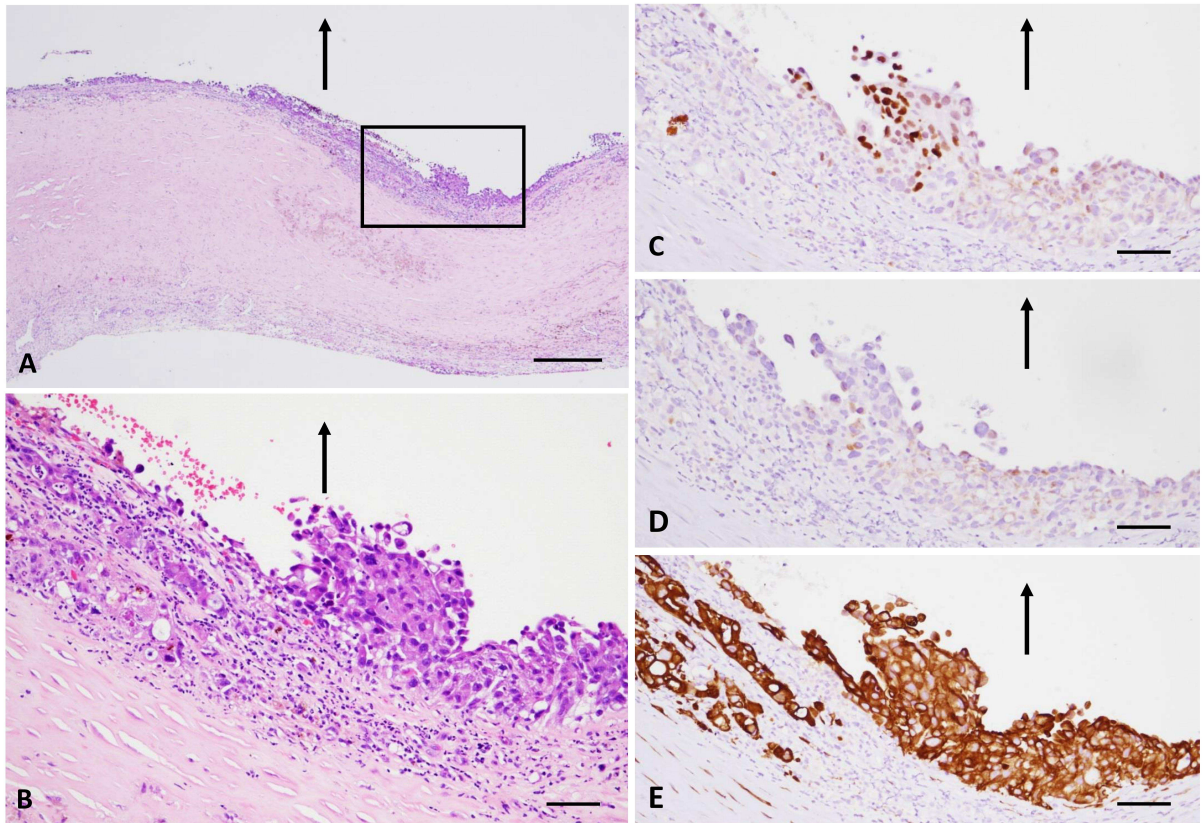
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Highlights

- We present a case of metastasis of a malignant tumor to the CSDH capsule.
- Metastasis to the hematoma capsule may cause short-term repeated recurrences of CSDH.
- CSDH due to metastasis to the hematoma capsule may be difficult to treat.