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Original Article

# Relationship between Transient Cortical Blindness and Contrast Medium Leakage That Occurs after Endovascular Treatment of Posterior Circulation Aneurysms

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**Objective:** The mechanism of transient cortical blindness after endovascular treatment—a rare phenomenon—has not been elucidated; however, it is assumed to be related to contrast medium leakage (CML). We investigated the relationship between postoperative CML and cortical blindness in patients who underwent endovascular treatment for vascular lesions of posterior circulation.

**Methods:** This retrospective cohort study included 28 patients who underwent endovascular treatment for posterior circulation aneurysms at our hospital between January 2014 and December 2018. Cerebral CT was performed immediately after endovascular treatment and 24 h later. CT images were retrospectively evaluated with special interest in the presence and distribution of leakage of the contrast medium (CM). Patients were classified into the following three groups based on CT findings: Group A, no CML (11 patients); Group B, unilateral CML (5 patients); and Group C, bilateral CML (9 patients).

**Results:** The posterior circulation aneurysms were located in the basilar artery in 13 (52.0%) cases, in the posterior cerebral artery in 1 (4.0%) case, and in the vertebral artery in 11 (44.0%) cases. There was no difference regarding the adjunctive technique used for endovascular treatment between the groups. Patients in Group C used a significantly larger amount of CM than those in the other two groups. A longer operation time was associated with a larger amount of CM used during treatment. VerifyNow assay revealed that the P2Y12 reaction unit was significantly lower in Groups B and C. Cortical blindness was transiently observed in 2 of 9 patients (22.2%) in Group C, both of which showed CML surrounding the bilateral parieto-occipital sulcus.

**Conclusion:** Both patients with cortical blindness showed bilateral CML, both of which showed CML surrounding the bilateral parieto-occipital sulcus. The CM-induced blood–brain barrier disruption may be the cause of cortical blindness.

**Keywords** contrast medium leakage, endovascular treatment, cortical blindness, posterior circulation

## Introduction

Transient cortical blindness after endovascular treatment is rare. The mechanism of occurrence has not been elucidated; however, contrast medium (CM)-induced blood–brain barrier (BBB) damage and neurotoxicity have been reported in patients with transient cortical blindness.[1,2] In addition, it has been suggested that BBB damage was identified by postoperative contrast medium leakage (CML).[1,2] According to these data, we hypothesized that CML might be the specific predictor for transient cortical blindness. If we could mitigate the risk factors for CML, BBB damages, such as cortical blindness, could be avoided after endovascular surgery. In this study, we investigated postoperative CML in patients who underwent endovascular treatment for posterior circulation aneurysms and evaluated the conditions and characteristics of patients with postoperative transient cortical blindness. We also examined whether CML is related to the endovascular techniques, type of CM, the total amount of CM used,

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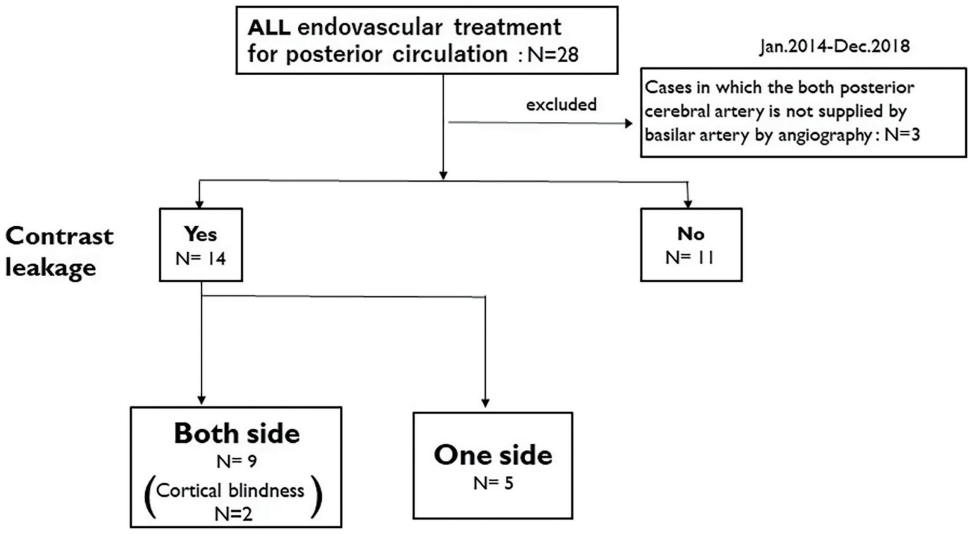


**Fig. 1** Patient flow in this study.

platelet function test by VerifyNow (Instrumentation Laboratory, Bedford, MA, USA) assay, and other factors.

## Materials and Methods

### Patient selection

This retrospective study involved 28 patients who underwent endovascular treatment for unruptured aneurysm in posterior circulation at our hospital between January 2014 and December 2018. We excluded 3 patients in whom both posterior cerebral arteries (PCAs) were not supplied by the basilar artery (BA), as observed on cerebral angiography (**Fig. 1**). Cerebral CT was performed immediately after endovascular treatment and the next day (within 24 hours). CML was defined as abnormal contrast enhancement of the cortex of the occipital lobe or leakage of the CM in the subarachnoid space, and was determined by comparing CT findings immediately and within 24 hours after treatment. All plain CT scans were reviewed independently by three doctors (two neuroradiologists and one neurosurgeon) with over 10 years of clinical experience who were not informed of the patient's clinical status. Patients were classified into the following three groups based on CT findings: Group A, no CML (11 patients); Group B, unilateral CML (5 patients); and Group C, bilateral CML (9 patients) (**Fig. 2**). Aspirin and clopidogrel were administered at doses of 100 and 75 mg for 14 days before endovascular treatment. In all cases, blood was collected for VerifyNow assay 2 days before surgery. For VerifyNow assay findings, if aspirin reaction units (ARU) are 550 or less and P2Y12 reaction units (PRUs) are 235 or less, it is judged to be effective. If the effect of VerifyNow assay findings was insufficient, cilostazol 100 mg/day was added. Vertebral angiography during embolization procedures was performed with injection of 4–6 mL of CM manually or using a power injector at a rate of 6 mL/second. Two types of CM, iohexol and iodixanol, were used. For manual angiography, the CM is diluted with heparinized saline. It was calculated assuming that 4 mL of CM was used in 1 injection. In all cases, 500 mg of methylprednisolone was used to prevent intraoperative CML by intravenous bolus injection at the start of treatment.

This study was approved by the ethics institutional review board of the Kurume University.

### Statistical analysis

Results are expressed as mean ± SD. Statistical significance was evaluated using the Fisher's exact test and for each pair by the Student's t-test. We examined the association of cortical blindness and CML. We used multivariable logistic regression to control for the potentially confounding roles of age, sex, procedure time, amount of CM, and VerifyNow assay findings. Analyses were performed using the JMP version 15 software package (SAS Institute, Cary, NC, USA).

## Results

We examined 25 patients with a mean age of 51 years and a women-to-men ratio of 12:13. Among 25 patients, 11 were classified into group A (no CML), 5 patients into

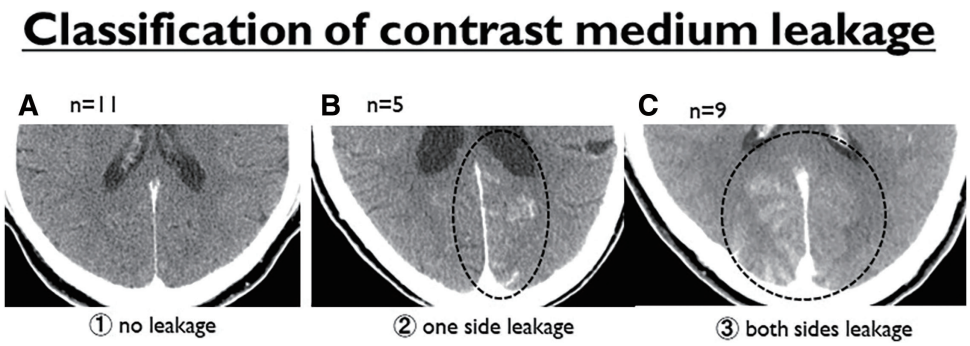


**Fig. 2** Classification of CML: Group A, no CML leakage (11 patients); Group B, unilateral CML leakage (5 patients); and Group C, bilateral CML leakage (9 patients). CML: contrast medium leakage

**Table 1** Demographics of patients with CML

| Characteristic | Total (N = 25) | | Both sides (n = 9) | | One side (n = 5) | | None (n = 11) | | p value |
|---|---|---|---|---|---|---|---|---|---|
| | ±SD | % | ±SD | % | ±SD | % | ±SD | % | |
| Mean age | 57.1 ± 11.4 | | 52.3 ± 12.8 | | 59.4 ± 10.1 | | 60.0 ± 10.3 | | 0.2958 |
| Sex (male) | 12 | 48.0 | 3 | 33.3 | 1 | 20.0 | 8 | 72.7 | 0.0719 |
| Laboratory data | | | | | | | | | |
| Platelet count | 24.1 ± 5.3 | | 22.2 ± 5.6 | | 23.9 ± 4.2 | | 25.8 ± 5.3 | | 0.5559 |
| INR | 0.96 ± 0.071 | | 0.95 ± 0.067 | | 0.97 ± 0.071 | | 0.99 ± 0.076 | | 0.6824 |
| aPTT | 27.9 ± 4.3 | | 28.2 ± 3.4 | | 25.4 ± 2.8 | | 28.9 ± 5.2 | | 0.2607 |
| Types of contrast media | | | | | | | | | |
| Iohexol | 11 | 44.0 | 6 | 66.7 | 1 | 20.0 | 4 | 36.3 | 0.1814 |
| Iodixanol | 14 | 56.0 | 3 | 33.3 | 4 | 80.0 | 7 | 63.6 | |

* p <0.05. aPTT: activated partial thromboplastin time; CML: contrast medium leakage; INR: international normalized ratio; SD: standard deviation

group B (unilateral CML), and 9 patients into group C (bilateral CML).

There were no significant differences in platelet count, prothrombin time-international normalized ratio (PT-INR), and activated partial thromboplastin time (APTT) among the three groups. Although iohexol was more frequently used in Group C (66.7%) than Group A (36.3) or Group B (20.0), there were no statistically significant differences between the groups (**Table 1**). The posterior circulation aneurysms were located in the BA in 13 (52.0%) cases, in the PCAs in 1 (4.0%) case, and in the vertebral artery (VA) in 11 (44.0%) cases. There was no difference regarding endovascular procedures and angiographical outcome between the groups. Details are shown in **Table 2**.

A significantly greater amount of CM was used in Group C than in the other two groups (**Fig. 3**). The procedure time was defined as the time from arterial puncture to removal of the guiding catheter.

It has a tendency that great amount of CM was used in the long-time procedure. CML was observed more frequently in patients in whom a greater amount of CM was used. Despite a short procedure time, one patient in Group C had CML (**Fig. 4**). Fourteen patients received over 160 mL of total CM injection, 12 of whom showed CML (85.7%); furthermore, in all 14 patients with CML, 12 patients (85.7%) received over 160 mL of CM in total. In the VerifyNow assay, the PRU was significantly lower in the CML-positive group (groups B and C: 169.2 ± 48.5, mean ± SD) than in the CML-negative group (group A: 215.8 ± 48, mean ± SD) (**Fig. 5**).

Case A had dissecting VA aneurysm. The aneurysm was treated with stent-assisted coil embolization using LVIS Jr. (Terumo, Tokyo, Japan). The procedure time was 130 minutes and 340 mL of iohexol was used. Cortical blindness was observed from 3 hours to 72 hours after the procedure. Case B had basilar tip aneurysm. The aneurysm was treated with stent-assisted coil embolization using LVIS Jr. The procedure time was 120 minutes and 280 mL of iohexol was used. Cortical blindness was observed from 2 hours to 72 hours after the procedure.

In both cases of cortical blindness, the symptoms of total blindness appeared several hours after the operation, gradually improving within 72 hours. Anosognosia such as

**Table 2** Endovascular treatment

| Characteristic | Total (N = 25) | | Both sides (n = 9) | | One side (n = 5) | | None (n = 11) | | p value |
|---|---|---|---|---|---|---|---|---|---|
| | n (±SD) | % | n (±SD) | % | n (±SD) | % | n (±SD) | % | |
| Location | | | | | | | | | |
| BA | 13 | 52.0 | 5 | 55.6 | 3 | 60.0 | 5 | 45.4 | 0.6152 |
| PCA | 1 | 4.0 | 0 | 0.0 | 0 | 0.0 | 1 | 9.1 | |
| VA | 11 | 44.0 | 4 | 44.4 | 2 | 40.0 | 5 | 45.5 | |
| Aneurysm morphology | | | | | | | | | |
| Saccular aneurysm | 17 | 68.0 | 6 | 66.6 | 3 | 60.0 | 8 | 72.7 | 0.9609 |
| Dissecting aneurysm | 8 | 32.0 | 3 | 33.3 | 2 | 40.0 | 3 | 37.5 | |
| Endovascular procedures | | | | | | | | | |
| Coil embolization | | | | | | | | | |
| Simple | 2 | 8.0 | 0 | 0.0 | 0 | 0.0 | 2 | 18.2 | 0.0666 |
| Double catheter | 5 | 20.0 | 0 | 0.0 | 2 | 40.0 | 3 | 27.3 | |
| Stent | 16 | 64.0 | 8 | 88.9 | 2 | 40.0 | 6 | 54.5 | |
| Attempt | 1 | 4.0 | 0 | 0.0 | 1 | 20.0 | 0 | 0.0 | |
| PAO | 1 | 4.0 | 1 | 11.1 | 0 | 0.0 | 0 | 0.0 | |
| Surgical result | | | | | | | | | |
| Complete | 18 | 72.0 | 6 | 66.7 | 3 | 60.0 | 9 | 81.8 | 0.4711 |
| Neck remnant | 5 | 20.0 | 2 | 22.2 | 1 | 20.0 | 2 | 18.2 | |
| Attempt | 1 | 4.0 | 0 | 0.0 | 1 | 20.0 | 0 | 0.0 | |
| PAO | 1 | 4.0 | 1 | 11.1 | 0 | 0.0 | 0 | 0.0 | |

* p <0.05. BA: basilar artery; PAO: parent artery occlusion; PCA: posterior cerebral artery; SD: standard deviation; VA: vertebral artery

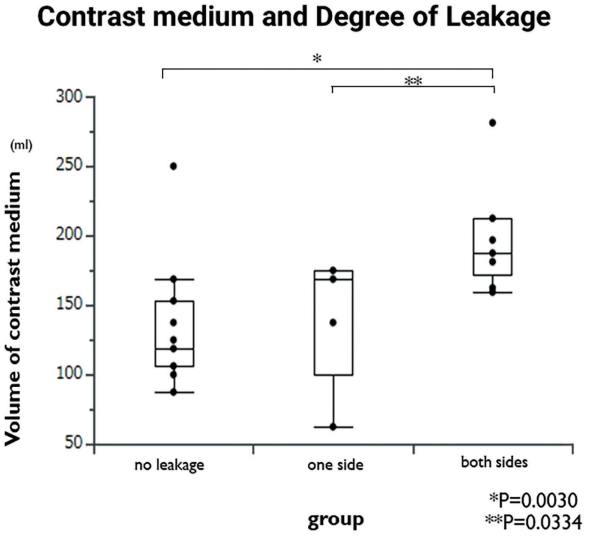


**Fig. 3** CM and degree of leakage. A significantly greater amount of CM was used in Group 3 than in the other two groups. CM: contrast medium

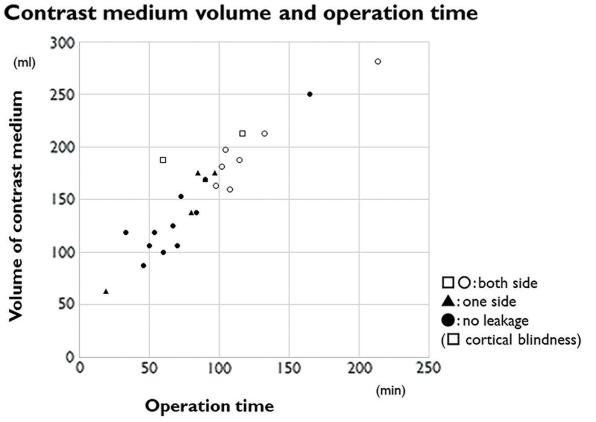


**Fig. 4** CM volume and operation time. Dot blot analysis, with the y axis indicating the volume of CM used in operating time and the x axis indicating the operation time. CM: contrast medium

Anton syndrome was also observed. The PRU value was 158 for Case A and 137 for Case B.

Transient blindness was observed in 2 of 9 patients classified into group C (22.2%). There were no patients with blindness in groups A and B. However, there was no obvious correlation between cortical blindness and the amount of CM used or operation time. In both patients presenting with transient blindness (cases A and B), the CML in and around the bilateral parieto-occipital sulcus was observed (**Fig. 6**).

MRI and single-photon emission CT (SPECT) were performed during the appearance of the blindness in both patients (cases A and B). MRI revealed no particular findings related to visual impairment such as cerebral infarction. In Case A, the cerebral blood flow (CBF) in the right occipital lobe was lower than that on the contralateral side. After symptom improvement, SPECT revealed no difference in CBF between the two sides. In Case B, no obvious decrease in CBF or laterality was observed (data not shown).

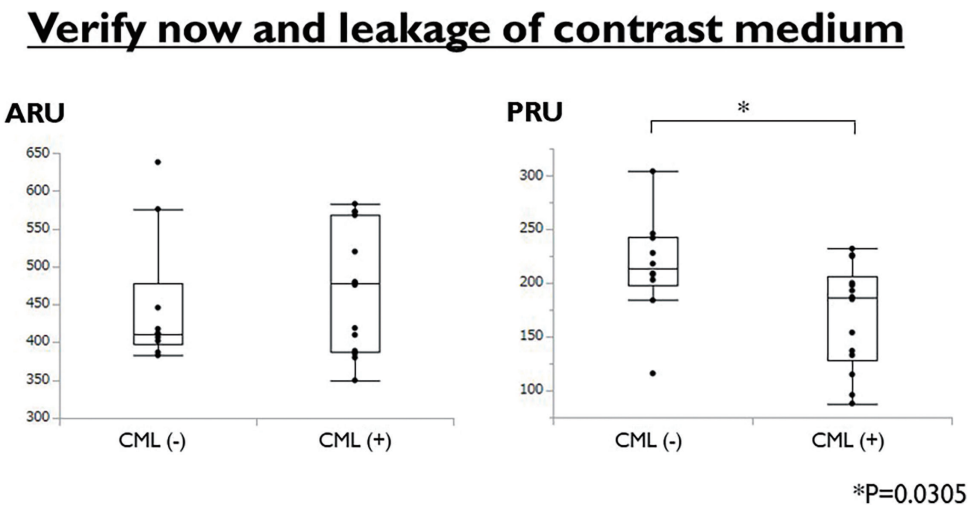


**Fig. 5** VerifyNow assay and leakage of CM. VerifyNow ARU and PRU assay findings with the leakage of CM. PRU assay findings were significantly lower in the group with CML. ARU: aspirin reaction unit; CM: contrast medium; CML: contrast medium leakage; PRU: P2Y12 reaction unit

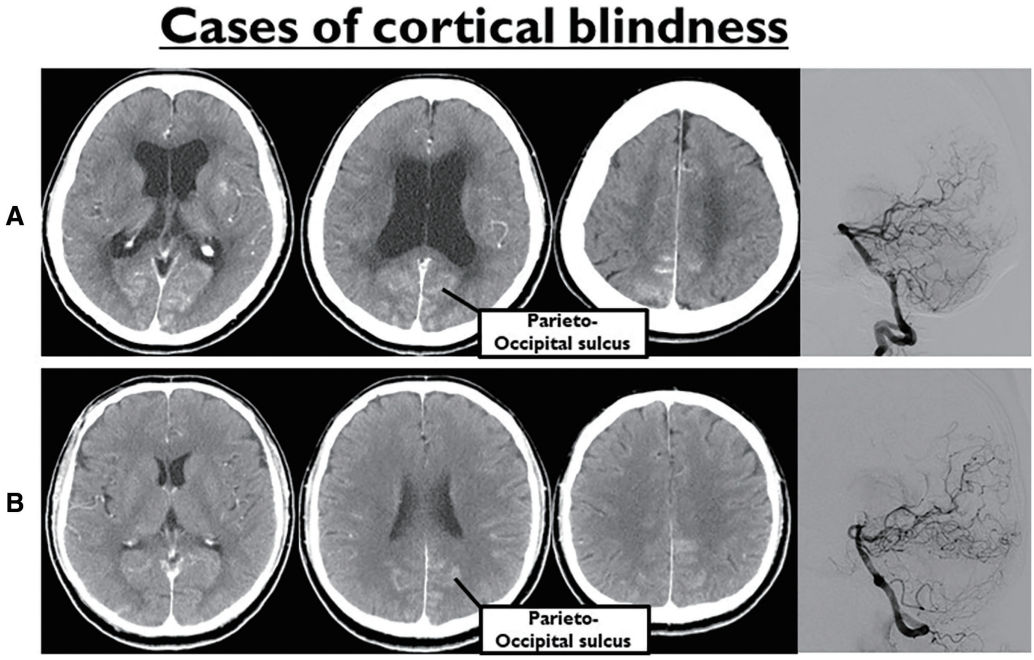


**Fig. 6** Case of cortical blindness. Two cases had bilateral CML around the parieto-occipital sulcus (**A** and **B**). CML: contrast medium leakage

## Discussion

### Mechanisms of CML

We previously reported a case presenting with CML after coil embolization for cerebral aneurysm and speculated that CM could damage the BBB resulting in CML.[3,4] In the present study, CML was observed in 14 of 25 patients, and the average dose of CM used was significantly greater in the CML-positive patient group than that in the CML-negative group. The procedure time tended to be longer in the CML-positive group than in the CML-negative group, but without a significant difference. The results of this study support our previous report that demonstrated that multiple CM injections within a short period could cause BBB destruction. Regarding the types of CM, iodixanol and iohexol were used in the patients involved in this study. The osmic pressure is lower for iodixanol than that for iohexol. Although iohexol was more

frequently used in Group C (66.7%) than in Group A (36.3%) or Group B (20.0%), there were no statistically significant differences between the groups.

Lou et al. reported that clopidogrel could inhibit the recovery of injured BBB based on the results of experiments using mice.[5] Specifically, clopidogrel antagonizes the P2RY12 receptor on microglial cells and consequently suppresses juxtavascular microglial cell activation involved in the protection and maintenance of the BBB. In the results of the present study, the PRU was significantly lower in CML-positive patients than in CML-negative patients. Clopidogrel may reduce microglial cells' ability to maintain BBB in a clinical setting.

### Characteristics and pathogenesis of cortical blindness related to CM

In the present study, the overall incidence of transient cortical blindness was 8.0% (2 of 25 patients). In both patients with transient cortical blindness, iohexol with osmic pressure higher than that of iodixanol was administered as a CM and bilateral CML was observed in and around the parietal-occipital sulcus. Several preceding studies on cortical blindness reported that it could occur after CM injection with an incidence of 0.3% to 1.0%. In most reported cases, cortical blindness was a transient symptom similar to our cases. Cases with permanent blindness were rarely reported.[1,2] The mechanisms of cortical blindness after CM injection have not yet been elucidated; however, several hypotheses were proposed. Most reports agree that CM-induced encephalopathy in the secondary visual area of the occipital lobes can cause cortical blindness.

The neurotoxicity of CM may be one of the major causes of posterior lobe injury. Some previous studies reported cortical and subarachnoid hyperdensities on contrast-enhanced CT in the patients with cortical blindness, and advocated that the CM could osmotically destroy the BBB, especially in the occipital lobe in which sympathetic innervation was different from other parts of the cerebral lobe.[6–11] CT images of our patients presenting transient cortical blindness showed similar findings to these reported findings. A larger amount of CM used was associated with CML as mentioned above; however, there was no obvious correlation between cortical blindness and the amount of CM used or operation time in the multivariate analysis of the present study.

Shinoda et al. reported a case with cortical blindness presenting CBF reduction in the bilateral occipital lobes on SPECT.[6] However, in the present cases, CBF in the occipital lobes had a unilateral reduction in case A and was normal in case B. These results suggest that cortical blindness does not always result from decreased CBF in bilateral occipital lobes.

According to the above discussions, it is suggested that CM-induced BBB breakdown in the bilateral occipital lobes resulting in cortical dysfunction is the cause of cortical blindness after coil embolization. A large amount of CM used, multiple CM injections in a short time, and the use of clopidogrel may be the incentive of CML associated with cortical blindness.

## Conclusion

CML is associated with a large amount of CM used in the embolization procedure. Cortical blindness may be related to CM-induced BBB disruption.

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## Disclosure Statement

The authors declare that they have no conflicts of interest.

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