RESEARCH ARTICLE

Diffusion-Restricted Lesions of the Splenium

Clinical Presentation, Radiographic Patterns, and Patient Outcomes

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Abstract

Background and Objectives

Diffusion-restricted (DR) lesions of the splenium are encountered in a wide variety of pathologies, and their significance is often unclear. We sought to report the spectrum of clinical presentations, neuroimaging patterns, and the predictors of radiographic and clinical outcomes from DR splenial lesions.

Methods

This was a single-center, retrospective cohort study from January 1, 2009, to August 1, 2020. A consecutive sample of 3,490 individuals who underwent brain MRI with reported corpus callosum lesions during the study period were evaluated for DR lesions in the corpus callosum. DR lesions were defined as increased signal intensity on diffusion-weighted imaging sequences with decreased signal intensity on apparent diffusion coefficient. Patients with prior neurosurgical procedures, hemorrhage-associated DR, anoxic brain injury, and chronic or previously known or characterized disease processes in the corpus callosum were excluded. Clinical and radiologic outcomes were ascertained, including readmissions within 1 year, in-hospital mortality rates, and resolution of DR at first follow-up imaging. Outcomes were defined a priori.

Results

Two hundred patients met criteria for inclusion. The average age was 57 years (standard deviation 19 years). Near half of the patients were women (47%). Encephalopathy (55%), focal weakness (46.5%), and cortical signs (44%) were the most common presenting clinical features. Thirty-five cases (17.5%) had features consistent with cytotoxic lesions of the corpus callosum (CLOCCs). Vascular causes were most frequent (61%), followed by malignancy-related (15%) and trauma (8%). In-hospital mortality occurred in 8.5% of cases, 46.5% were readmitted to the hospital within 1 year, and 49.1% of patients had resolution of the splenial DR at the next scan. Backward stepwise regression models showed that mass effect was negatively associated with splenial DR resolution (odds ratio [OR]: 0.12, confidence interval [CI] 0.03–0.46, $p = 0.002$). Encephalopathy was significantly associated with in-hospital mortality (OR: 4.50, CI 1.48–17.95, $p = 0.007$). Patients with a CLOCC had less frequent readmissions at 1-year compared with patients without a CLOCC, $p = 0.015$.

Discussion

Vascular DR lesions of the splenium were more common than CLOCCs and other etiologies in this cohort. While splenial DR lesions can present a clinical challenge, their associated clinical and radiographic characteristics may predict outcome and guide prognosis.

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Introduction

Lesions of the corpus callosum—particularly those that demonstrate diffusion restriction (DR) in the splenium—have a broad range of etiologies[1,2] and generate clinical uncertainty. Splenial DR can be due to neoplasm, vascular disorders, infections, demyelinating disorders, trauma, and many other etiologies.[2] Although ischemic infarction is always an important consideration in the differential diagnosis of DR, infarction of the corpus callosum is relatively rare, accounting for only 3%–8% of all infarcts.[3] This infrequency of presentation is believed to be secondary to the corpus callosum's abundant blood supply (from both the anterior and posterior circulations), arising from 3 main arterial systems, namely the anterior communicating, anterior cerebral, and posterior cerebral arteries.[4,5] Infarctions of the corpus callosum are white matter strokes and may be unilateral, bilateral, or midline. Most of the callosal infarctions involve the splenium,[2] which is supplied by the posterior pericallosal branch of the posterior cerebral artery.[5] More recently, COVID-19 has been associated with infarction of the central splenium of the corpus callosum,[6] and clusters of these rare splenial infarcts have been seen with COVID-19 infection.[7]

Over time, increasing attention has been paid to the reversible splenial lesions,[8] which have been referred to by different names, including "mild encephalopathy with reversible splenial lesions (MERS)"[9] and "reversible splenial lesion syndrome (RESLES)."[10] However, the earlier terminologies had limitations given the fact that (1) the accompanying encephalopathy is not always mild (can range from absent to severe)[11,12] and (2) the splenial DR lesions are not invariably reversible.[11,12] As such, the lesions have more recently been called cytotoxic lesions of the corpus callosum (CLOCCs). CLOCCs are typically midline, relatively symmetric, usually located in the splenium, and often, but not always, reversible.[12] These lesions have been associated with brain trauma, metabolic derangements, subarachnoid hemorrhage, infection (e.g., viral encephalitis), and certain medications or drug exposures, namely toxicity or withdrawal of antiseizure drugs, among many other conditions.[12-14]

While callosal DR lesions are overall rare,[1] and CLOCCs are generally confined to case reports[15,16] and small case series,[17] the broad range of potential etiologies underscores the relevance of these lesions across an expansive list of differential diagnoses. The limited available systematic data to guide characterizing[2] and predicting outcomes for callosal DR lesions has been daunting for clinicians, neurologists, and neuroradiologists alike. Thus, we sought to report on the spectrum of clinical presentations, neuroimaging patterns, and the predictors of radiographic and clinical outcomes in DR splenial lesions.

Methods

We identified a retrospective clinical cohort study of patients with DR within the splenium of the corpus callosum. We searched the radiology databases at our institution using the search terms "corpus callosum" or "splenium of corpus callosum" and "diffusion restriction" that were generated between January 1, 2009, and August 1, 2020. The first author then systematically reviewed all images and corresponding radiology reports to identify patients with DR in the splenium. Diffusion-restricting lesions were defined by increased signal intensity on diffusion-weighted imaging (DWI) sequences with decreased signal intensity on apparent diffusion coefficient (ADC). Patients with prior neurosurgical procedures, recent cardiac procedures, hemorrhage-associated DR (defined as acute hemorrhage overlapping the area of splenium DR), diffuse anoxic brain injury, and chronic or previously known and characterized disease processes were excluded. The collection of patients with splenial DR and the collection of those excluded were independently reviewed by the lead author (neurologist) before proceeding to the next phase of data collection. The medical records from patients meeting inclusion criteria then underwent systematic data abstraction by BS, CL, MT, and DTJ. Uniformity of abstraction was maintained by (1) creation of a data dictionary that defined all variables and potential range of values and (2) multiple quality control checks, including a review by the lead author of several random records that had been reviewed by each respective reviewer at the beginning of the chart abstraction process, as well as review of the overall data set by the lead author after chart abstraction was complete. This study follows STROBE guidelines for observational studies.

The following categories of variables were included in the systematic data abstraction: demographics, medical history, medications on admission, presenting neurologic symptoms and signs, laboratory data, and radiologic features, including regions of corpus callosal DR, pattern of splenial involvement, other areas of DR, as well as other radiologic findings. Specific note was made if the splenial DR lesions conformed to the pattern of a CLOCC, according to the characteristics described by Starkey et al.[12] Specifically, Starkey et al. provided contemporary radiographic definitions of CLOCCs as lesions fulfilling one of the 3 following patterns: (1) a small round/oval lesion centered in the splenium, (2) a lesion located in the center of the splenium extending laterally through the callosal fibers into nearby white matter, or (3) a lesion centered posteriorly in the splenium extending into the anterior corpus callosum. Furthermore, CLOCCs lack enhancement on gadolinium-enhanced MRI imaging, are typically midline and relatively symmetric, although some forms may be asymmetric. While CLOCCs are frequently reversible on repeat imaging, this is not uniformly the case,[11,12] and thus, reversibility on imaging was not used to define CLOCCs in our study. MRI scans were performed using either the 1.5-T or 3-T scanners at our institution. At a minimum, each scan included T1, T2, FLAIR, DWI, and ADC sequences. Additional sequences—if ordered by the treating clinical team—included gadolinium-enhanced T1, gradient echo, and/or susceptibility-weighted imaging. All images had a formal neuroradiology report completed at the time of the imaging. The images and the

Table 1 Baseline Demographic, Clinical, and Radiologic Characteristics of Patients With Diffusion Restriction in the Splenium of the Corpus Callosum

Demographics, n (%)	
Average age, y	57 ± 19
Women	94 (47)
White	108 (56.0)
Black or African American	64 (31.1)
Hispanic or Latino	23 (11.2)
Other	15 (7.8)
Unknown[a]	7 (3.6)
Medical history, n (%)	
Malignancy	53 (26.8)
History of stroke or TIA	41 (20.7)
Myocardial infarction and/or coronary artery disease	39 (19.7)
Presenting symptoms and signs, n (%)	
Encephalopathy	110 (55)
Focal weakness	93 (46.5)
Cortical signs[b]	85 (44.0)
Headache	68 (34.8)
Seizure	26 (13)
Hypoesthesia	17 (8.8)
Paresthesia	14 (7.3)
Radiologic features, n (%)	
Regions of diffusion restriction	
Splenium + other subcortex	150 (75)
Multifocal pattern	143 (71.5)
Splenium + cortex	132 (66)
Splenium plus other areas of the CC	40 (20.2)
Splenium only	31 (15.7)
Body involved	34 (17.1)
Genu involved	13 (6.5)
Rostrum involved	4 (2.0)
Pattern of splenial diffusion restriction	
Lateralized	140 (72.2)
Midline	60 (30.9)
Features consistent with CLOCC	35 (17.5)
Other radiologic findings	
T2/FLAIR lesions	175 (87.5)
Gadolinium enhancement	56 (31.1)
GRE or SWI lesions	60 (30.6)
Mass effect	45 (22.5)
IPH or IVH	23 (11.5)

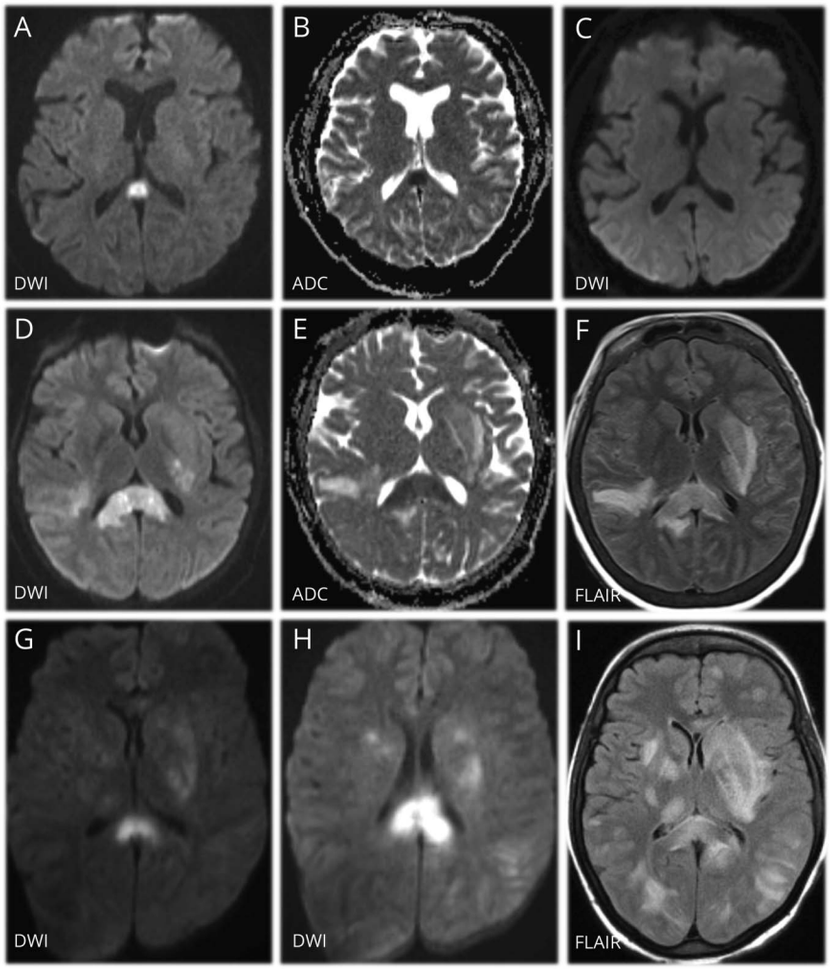
Abbreviations: GRE = gradient echo; IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage; SWI = susceptibility weighted imaging.
All statistics presented as either mean ± standard deviation or n (%).
[a] Unknown included unknown, unable to answer and declined.
[b] Cortical signs included homonymous visual field deficits, aphasia, apraxia, agnosia, and alexia.

formal reports were reviewed during chart abstraction. The most likely etiology for the splenial DR in each case, as documented by the treating clinical team, was also recorded. For example, a case was deemed to be of vascular etiology when the treating team documented a vascular process, e.g., posterior cerebral artery infarction involving the splenium, at the top of their differential diagnosis in the electronic medical record. For vascular cases, the most likely stroke mechanism was categorized according to the TOAST criteria,[18] as documented by the treating clinical team. Clinical and radiologic outcomes, including readmissions within 1 year, in-hospital mortality rates, and resolution of DR at the time of first follow-up MRI imaging, were also ascertained.

Descriptive statistics for demographics, medical history, presenting symptoms and signs, and the radiologic features of the splenial lesions were generated. Sixteen clinically relevant variables were selected as potential predictors of the outcomes. These variables were age at diagnosis, sex, White vs non-White race, ≥1 vascular risk factor, history of cancer, presenting symptoms (including seizure, headache, encephalopathy, and focal weakness), atrial fibrillation on electrocardiogram, radiographic features (including splenium DR only, splenium DR plus other regions of the corpus callosum, intraparenchymal hemorrhage or intraventricular hemorrhage, mass effect, and gadolinium enhancement), and vascular etiology.

We looked at the unadjusted association between the 16 eligible predictors—chosen a priori—and the 3 primary outcomes (eTable 1, links.lww.com/CPJ/A462). Backward stepwise regression was used to identity the set of variables that best modeled each outcome. This process required complete cases for each combination of outcome and the 16 predictors. Once the set of predictors was selected, a new set of complete cases was identified, only based on the outcome and final set of predictors. These complete cases were used in logistic regression models to estimate the odds ratio (OR) for the outcome associated with the predictor, adjusted for the other variables in the model. Owing to the rare occurrence of in-hospital mortality within the sample (<10%), the

Figure 1 Typical Cytotoxic Lesion of the Corpus Callosum (CLOCC) Imaging Appearances



Row 1 depicts a midline, ovoid region of diffusion restriction in the splenium (A, B) with resolution 15 days later (C) in a patient with neuroleptic malignant syndrome. Row 2 shows imaging from a patient with hemophagocytic lymphohistiocytosis (HLH) with a CLOCC centered in the splenium but branching out bilaterally within the callosal fibers (D, E, F). Row 3 depicts imaging from a patient with tacrolimus-associated posterior reversible encephalopathy syndrome (PRES). This CLOCC is centered posteriorly within the splenium (G) but also extends more anteriorly within the corpus callosum (H) and has the associated confluent T2/FLAIR changes seen in PRES (I).

Firth correction was applied to this outcome.[19] Note that the number of records used for stepwise regression was consistently smaller than the number of records used in the model because of the shifting criteria for completeness. After estimating the OR and 95% CI for each predictor, we calculated the area under the curve for each model to capture model fit.

Finally, to determine the relationship between the primary outcomes—including splenium DR and 1-year readmission—and the occurrence of CLOCC, we looked at the frequencies between each pair. We removed the records with in-hospital mortality (n = 17) and removed records with either outcome missing from the analysis. Chi-square tests were used to determine whether there was an association between CLOCC and the other 2 outcomes.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Institutional Review Board at our institution (study number STU00210797).

Data Availability

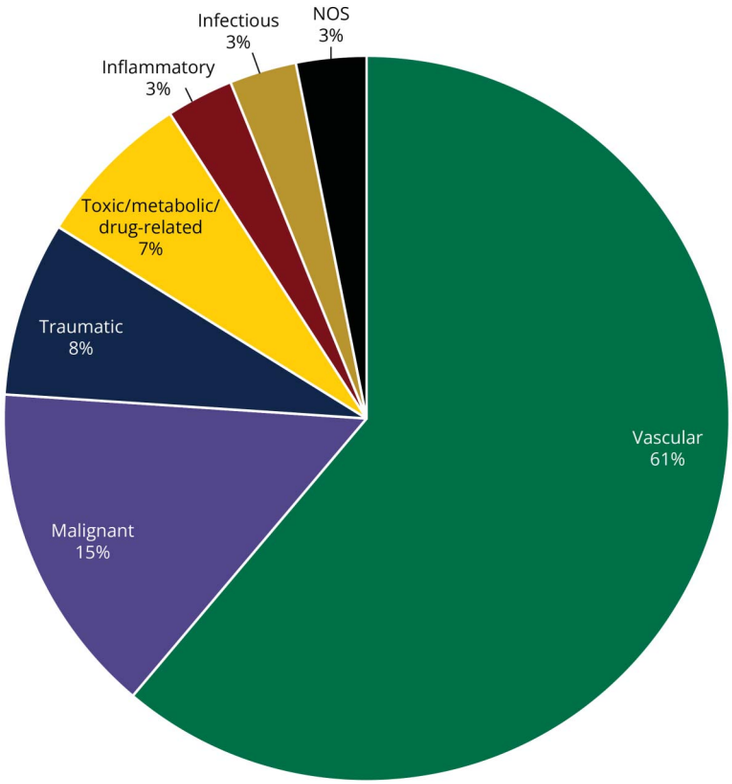
The data are not publicly available because study participants did not consent for this availability.

Results

The initial search yielded 3,490 individuals who underwent brain MRI with reported lesions in the corpus callosum. After inclusion and exclusion criteria were applied, 200 patients with DR lesions of corpus callosum were identified for systematic data abstraction. See eFigure 1 (links.lww.com/CPJ/A461) for inclusion and exclusion flow diagram.

The demographic, medical history, and presenting symptoms and signs of the study cohort are listed in Table 1. The average age was 57 years, and 47% of the patients were women. In this cohort, 56.0% were White, 31.1% Black or African American, 11.2% Hispanic or Latino, and 7.8% from other races. For 3.6% of cases, race was unknown. Encephalopathy (55%, 95% CI

Figure 2 Proportions of Broad Diagnostic Etiologies of Splenial Diffusion Restriction Within the Study Population



48.1–61.9), focal weakness (46.5%, 95% CI 39.6–53.4), and cortical signs (44%, 95% CI 37.0–51.0) were the most common clinical features. More specifically, cortical signs included visual field deficits (25%), aphasia (21.5%), alexia (2.5%), apraxia (2%), and agnosia (1%).

Only 15.7% (95% CI 10.6–20.7) of cases had DR solely within the splenium of the corpus callosum, and midline splenial DR occurred in 30.9% (95% CI 24.4–37.4) of all cases. Thirty-five cases (17.5%, 95% CI 12.2–22.8) had features consistent with cytotoxic lesions of the corpus callosum (CLOCCs), such as those illustrated in Figure 1. DR in the splenium was often accompanied by DR in other regions of the brain, including the cortex (66%, 95% CI 59.4–72.6). Additional accompanying radiologic findings are listed in Table 1.

Vascular causes made up most of the etiologies (61%), followed by malignancy-related (15%), trauma (8%), and the other etiologic categories illustrated in Figure 2. Inpatient mortality occurred in 8.5% (95% CI 4.6–12.4), 46.5% (95% CI 39.6–53.4) were readmitted to the hospital within 1 year, and 49.1% (95% CI 39.6–58.5) of patients had resolution of the splenial DR at time of first follow-up scan. 108 patients (54%) had this follow-up imaging data available, and the median follow-up time was 15 days with a range of 1–2,082 days. Among vascular cases, stroke mechanisms included cardioembolism (29.8%), large-artery atherosclerosis (18.5%), multiple determined etiologies (16.9%), stroke of other determined etiology (14.5%), stroke of undetermined etiology (14.5%), and small vessel occlusion (5.6%).

In the unadjusted model, the following variables were found to have significant associations with the outcomes. The presence of mass effect (OR 0.08, 95% CI 0.02–0.28) and gadolinium enhancement (OR 0.41, CI 0.17–0.98) were associated with decreased odds of splenium DR resolution at the first follow-up scan. The following variables were associated with increased odds of 1-year readmission: age at diagnosis (OR 1.02, CI 1.00–1.03), ≥1 vascular risk factor (OR 2.10, CI 1.01–4.37), mass effect (OR 2.26, CI 1.14–4.46), and gadolinium enhancement (OR 2.26, CI 1.18–4.30). The following were associated with increased odds of in-hospital mortality: seizure (OR 3.31, CI 1.03–9.60), encephalopathy (OR 3.71, CI 1.23–14.68), and vascular etiology (OR 4.03, CI 1.20–20.79). These results are found in eTable 1 (links.lww.com/CPJ/A462).

In the adjusted multivariable regression models, mass effect was associated with decreased odds of splenial DR resolution (OR 0.07, CI 0.02–0.28); presence of ≥1 vascular risk factor with increased odds of 1-year readmission (OR 3.04, CI

Table 2 Logistic Regression Analysis Using Predictors Identified Through Backward Stepwise Regression to Model Outcomes From Diffusion Restriction in the Splenium of the Corpus Callosum

A	Splenium DR resolved		
Selected independent variables	OR	95% CI	*p* Value
AFIB on EKG	0.67	0.1–4.67	0.68
Mass effect	0.07	0.02–0.28	<0.001
Vascular etiology	0.52	0.19–1.44	0.207
AUC with 95% CI	0.73 (0.64–0.82)		
B	1-Year readmission		
Selected independent variables	OR	95% CI	*p* Value
CV risk factor	3.04	1.33–6.95	0.009
Seizure	1.76	0.73–4.23	0.205
Vascular etiology	0.56	0.29–1.07	0.080
AUC with 95% CI	0.62 (0.55–0.70)		
C	In-hospital mortality		
Selected independent variables	OR	95% CI	*p* Value
Encephalopathy	4.5	1.48–17.95	0.007
Splenium - other	0.08	0–0.59	0.008
AUC with 95% CI	0.75 (0.66–0.83)		

Abbreviations: 95% CI = 95% confidence interval; AUC = area under the curve; OR = odds ratio.
Complete cases used for variable selection: N = 78 (A), 146 (B), 147 (C); complete cases used for regression: N = 94, 195, 197.

1.33–6.95); and encephalopathy with increased odds (OR 4.50, CI 1.48–17.95) of in-hospital mortality. These results are found in Table 2.

Finally, patients with a CLOCC had less frequent readmissions at 1 year (12%) compared with patients without a CLOCC (88%), $p = 0.015$, as found in eTable 2 (links.lww.com/CPJ/A463).

Discussion

In this study, we report the frequency of diverse etiologies for splenial DR and characterize the clinical and radiologic features of these lesions. In addition, we identify the predictors of clinical and radiologic outcomes for splenial DR. We show that vascular etiologies were the most common reason for splenial DR. This is a significant finding with implications for acute treatments, inpatient evaluations, and secondary prevention of ischemic disease. The next 2 most frequent etiologic categories for splenial DR were malignancy—largely consisting of glioblastoma and CNS lymphoma—and trauma, which is consistent with the relative frequencies previously reported.[2,20] Thus, the overwhelming majority of the splenial DR lesions in our cohort were due to persistent or progressive intraparenchymal pathologies (e.g., ischemic infarcts and malignancies), rather than classically reversible etiologies, e.g., CLOCCs. This finding can have major implications for clinicians, who must conduct an appropriately thorough investigation to rule out vascular and malignant etiologies for splenial DR lesions before attributing these to CLOCCs, which may be reversible.

We systematically analyzed the clinical and radiographic characteristics of a large number of patients with splenial DR lesions and found that certain characteristics were associated with outcomes. This information may help guide decision-making when such lesions are encountered clinically. Clinically, we found that encephalopathy was positively associated with in-hospital mortality. This is consistent with previous literature, in which encephalopathy has been associated with mortality and morbidity in a number of different disease states.[21-23] However, the presence of a MERS has previously been associated with a mild clinical course, with all 15 patients studied having recovered completely within a month.[9] Our findings suggest that in the overall population of patients with splenial DR lesions, encephalopathy may not be so benign. This finding is specifically notable because encephalopathy was also the most frequent clinical characteristic in our cohort, affecting over half of the patients.

Radiographically, we found that specific features of the splenial DR lesions were associated with outcomes. For instance, the presence of mass effect was associated with lower odds of splenial DR resolution. This finding has biological plausibility because mass effect tends to be associated with space-occupying processes, such as tumors, which tend to be more progressive. It may also be seen in other primary etiologies, such as large ischemic or hemorrhagic infarcts, which again, tend to have a more aggressive course,[24] at least initially. In addition, in the unadjusted analysis, gadolinium contrast enhancement was also found to be negatively associated with splenium DR resolution and positively associated with readmission within a year. This finding follows a similar logic, given that intracranial contrast enhancement is associated with a wide variety of pathologies, many of which similarly tend to be progressive, such as primary neoplasms, metastases, and various infectious or inflammatory states,[25] whereas CLOCCs lack contrast enhancement.[12] This is an important distinction, particularly because malignancy was the second most frequent etiology for splenial DR lesions. The presence of mass effect or contrast enhancement should thus prompt further workup and follow-up.

Previous literature on CLOCCs is largely limited to single case reports[15,16] or small series,[17] which may be partially due to the rarity of these lesions. One of the hallmarks of CLOCCs is their frequent reversibility on imaging, which has been previously reported to occur within 1 month and usually within 1 week.[14] Furthermore, clinical outcomes

from midline splenial lesions are generally believed to be favorable,[11] but no previous large cohort study has systematically evaluated such radiographic and clinical outcomes. This study reports the frequency of splenial lesions with characteristics consistent with CLOCCs, with 35 cases (17.5%) fulfilling the criteria outlined before.[12] While most of the CLOCCs in our study had resolution of splenial DR, this was not uniformly the case. In addition, our finding that patients with radiographic features of CLOCC had less frequent readmissions at 1 year compared with patients without CLOCC, may also assist with prognostication in these patients.

Our study has important limitations to consider. First, this was a retrospective study, and it is possible that some cases of splenial DR were not captured by the search criteria used. We attempted to minimize this limitation by using a broad search strategy and only subsequently narrowing the list of included cases based on the presence of true DR in the splenium. However, because our definition of splenial DR included hypointensity on ADC, some patients with subacute stroke might have been excluded. Thus, the findings from this study can potentially underestimate the frequency of vascular causes for splenial lesions. Second, the retrospective nature prevents standardization of follow-up imaging. For instance, the time to first follow-up imaging was not uniform across patients and may have affected the respective probabilities of diffusion restriction resolution. In addition, only 54% of patients had follow-up imaging data available. Future prospective studies on splenial DR might help overcome the limitation of our study; however, the overall low incidence of splenial DR lesions will challenge the design of such future studies. Third, the study was conducted at a single academic, tertiary care center, which may be biased toward a more medically complex patient population, thus potentially limiting the generalizability of the results.

In this retrospective cohort of patients with splenial DR lesions, persistent or progressive etiologies, namely vascular and malignancy were more common than CLOCCs. Our findings have significant clinical implications for workup and management of these patients. In addition, we provide details of clinical features and radiologic characteristics of splenial DR lesions that will inform prognosis in the context of short-term and long-term outcomes.

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Behnam Sabayan, MD, PhD	Neurology, HealthPartners Institute, Minneapolis, MN	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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