

Histopathology-Informed Modeling of a Demyelinating Lesion Spectrum: Multiple Sclerosis, Baló's Concentric Sclerosis, and Tumefactive Demyelinating Lesions

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Histopathology-Informed Modeling of a Demyelinating Lesion Spectrum: Multiple Sclerosis, Baló's Concentric Sclerosis, and Tumefactive Demyelinating Lesions

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Abstract

Background: Baló’s concentric sclerosis (BCS) is a rare inflammatory demyelinating disorder characterized by concentric layers of alternating demyelinated and relatively myelin-preserved tissue. BCS shares pathological and radiological features with multiple sclerosis (MS) and tumefactive demyelinating lesions (TDLs). However, it remains unclear whether MS, BCS, and TDLs belong to a shared mechanistic spectrum.

Methods: We developed a seven-variable reaction–diffusion model incorporating resting and activated macrophages and microglia, normal and damaged oligodendrocytes, pro-inflammatory and anti-inflammatory cytokines, and a neuroprotective astrocyte-like component. We used sensitivity analyses to test whether parameter variations could generate MS, BCS, and TDL patterns. We compared simulated BCS patterns with quantitative radial profiles of Klüver–Barrera-stained sections from three autopsy BCS cases and examined post-onset modulation of selected lesion-promoting and protective pathways.

Results: Within a single framework, the model generated MS, BCS, and TDL patterns. Increasing either oligodendrocyte vulnerability or the inflammatory activity of macrophages and microglia shifted lesion morphology from the small MS pattern through the concentric BCS pattern to the broadly expanding TDL pattern, with the BCS pattern emerging mainly at intermediate values. The simulated BCS pattern exhibited several spatial features similar to those observed in pathological specimens. Earlier interventions produced greater suppression of lesion expansion than delayed interventions, while enhancement of protective or anti-inflammatory pathways also reduced lesion expansion.

Conclusions: These findings support the possibility of a shared mechanistic spectrum across MS, BCS, and TDLs. Oligodendrocyte vulnerability and the inflammatory activity of macrophages and microglia may contribute to the formation of demyelinating lesion patterns. The simulations further suggested that earlier intervention and enhancement of protective or anti-inflammatory pathways may more effectively suppress lesion progression. This framework may provide a clinically relevant perspective for interpreting BCS and TDLs in relation to MS.

Keywords: Multiple sclerosis, Baló’s concentric sclerosis, Tumefactive demyelinating lesions, Mathematical modeling, Histopathology, Microglia, Oligodendrocytes, Cytokines, Astrocytes

1 Background	093
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1.1 Multiple sclerosis and related demyelinating diseases	095
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1.1.1 Multiple sclerosis (MS)	098
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MS is the most common inflammatory demyelinating disease of the central nervous	100
system, characterized by multiple ovoid lesions, often located in periventricular regions	101
[1, 2]. Histopathologically, MS is characterized by focal inflammatory demyelinating	102
plaques, in which macrophages and microglia are often enriched at the edges of active	103
lesions [3] (Fig. 1A, D, F, and G).	104
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Disease-associated heterogeneity of oligodendrocyte lineage cells has also been re-	107
ported in MS, and oligodendrocyte-intrinsic factors have been proposed to influence	108
their susceptibility to injury [4, 5]. Although far less common than MS, Baló’s concen-	109
tric sclerosis (BCS) and TDLs may represent related manifestations within a shared	110
disease spectrum [6].	111
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1.1.2 Baló’s concentric sclerosis (BCS)	117
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BCS is an extremely rare demyelinating disorder, defined by concentric ring-like de-	119
myelinating lesions [7, 8] (Fig. 1B). Histopathologically, BCS is characterized by	120
prominent oligodendrocyte apoptosis and degeneration and early selective loss of	121
myelin-associated glycoprotein with relative preservation of other myelin proteins [9].	122
Astrocytes and microglia are also involved in the pathogenesis of BCS; astrocyte and	123
microglial activation has been observed within concentric lesions [10–12]. In addition,	124
myelin staining intensity tends to increase from the lesion center toward the periph-	125
ery [13, 14]. However, the mechanism underlying concentric ring formation remains	126
unclear.	127
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1.1.3 Tumefactive demyelinating lesions (TDLs)

TDLs are large demyelinating lesions with a tumor-like appearance and can occur in patients with MS [15, 16]. Histopathology typically shows active inflammatory demyelination with hypercellularity, inflammatory infiltrates, reactive astrocytosis, and numerous foamy macrophages containing myelin debris. These findings overlap with those seen in conventional inflammatory demyelination and are not specific to TDLs [15].

1.1.4 Common features among MS, BCS, and TDLs

In our previous study, patients with BCS showed clinical features similar to those observed in MS [17]. In addition to these clinical similarities, these inflammatory demyelinating lesions appear to share pathological features, including prominent involvement of macrophages and microglia at advancing lesion edges. MS is characterized by focal inflammatory demyelinating plaques, in which macrophages and microglia are often enriched at active lesion edges [3]. In BCS, activated microglia accumulate in the outermost demyelinating layer, suggesting a potential role for microglia in lamellar evolution [12]. Representative magnetic resonance imaging (MRI) and pathological findings from our cases illustrate these lesion phenotypes. The pathological findings show accumulation of macrophages and microglia at the lesion edge in MS and within the outermost lamella in BCS (Fig. 1). Although comparable pathological TDL specimens were unavailable, a previous MRI–pathology correlation study suggested macrophage infiltration at the inflammatory lesion border of TDLs [18].

1.2 Previous mathematical models

Several mathematical models have been proposed to generate concentric ring patterns of BCS using Turing- or chemotaxis-driven mechanisms [19–23]. Although these models can generate concentric rings, they do not explicitly reproduce several spatial

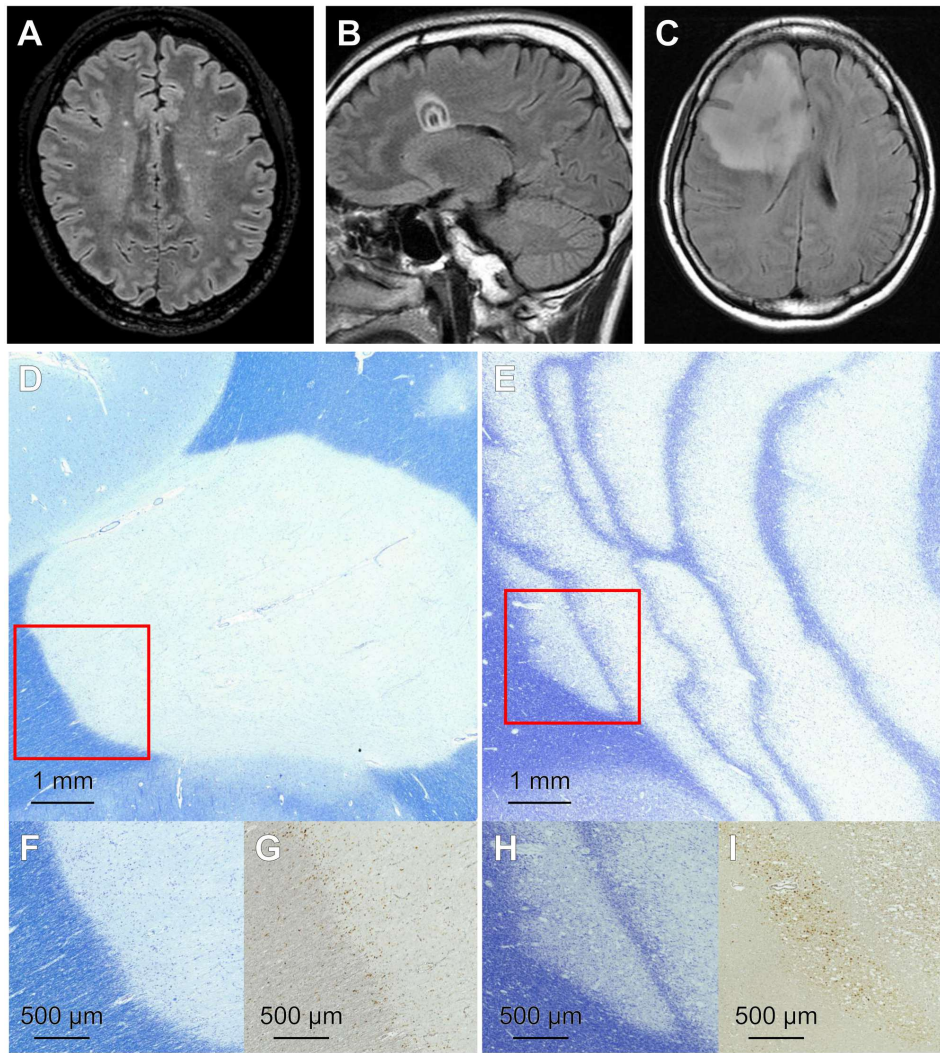


Figure 1 Representative MRI and histopathological findings in multiple sclerosis, Baló's concentric sclerosis, and tumefactive demyelinating lesions. (A) Multiple sclerosis (MS) (female, 30 years): fluid-attenuated inversion recovery (FLAIR), axial, showing ovoid periventricular lesions approximately 3–4 mm in diameter, oriented perpendicular to the lateral ventricles. (B) Baló's concentric sclerosis (BCS) (male, 29 years): FLAIR, sagittal, showing a concentric lesion with a maximum diameter of 18 mm. (C) Tumefactive demyelinating lesion (TDL) (female, 40 years): FLAIR, axial, showing a large lesion with a maximum diameter of 68 mm. (D, F, G) Histopathological findings of an MS lesion (male, 55 years). (D) Klüver-Barrera (KB) staining shows a sharply demarcated demyelinated plaque. (F) Magnified view of the red-boxed region in (D), showing the lesion edge. (G) Corresponding CD68 immunohistochemical staining shows accumulation of CD68-positive macrophages and microglia at the lesion edge. (E, H, I) Histopathological findings of a BCS lesion (female, 43 years). (E) KB staining shows alternating demyelinated and relatively myelin-preserved lamellae. The lesion center is located toward the upper right. (H) Magnified view of the red-boxed region in (E), showing alternating lamellae. (I) Corresponding CD68 immunohistochemical staining shows accumulation of CD68-positive macrophages and microglia in the outermost demyelinating lamella. Scale bars: (D, E), 1 mm; (F–I), 500 μ m.

231 features observed in BCS pathology. In these models, macrophage and cytokine pro-
232 files often show multiple internal peaks and do not match the outer-rim enrichment
233 of macrophages and microglia observed in BCS pathology [12]. They also do not re-
234 produce asymmetric myelin profiles across lamellae, including a radial trend toward
235 higher myelin-related signals in more peripheral, relatively myelin-preserved layers
236 [13, 14].
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241 242 **1.3 Aim of this study** 243

244 Given the proposed relationship among MS, BCS, and TDLs, we hypothesized that
245 quantitative variation in oligodendrocyte vulnerability and in the inflammatory activ-
246 ity of macrophages and microglia could generate distinct lesion patterns corresponding
247 to these three entities.
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251 We developed a unified mathematical model to test whether the MS, BCS, and
252 TDL patterns could arise from a common mechanism within a single model frame-
253 work. By comparing model outputs with quantitative histopathological measurements
254 from BCS lesions, we assessed whether the model reproduced key spatial features of
255 BCS pathology and examined parameter-dependent transitions among the three lesion
256 patterns.
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261 As an exploratory extension, we examined whether post-onset modulation of
262 selected inflammatory and protective pathways altered lesion expansion.
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266 **2 Methods** 267

268 **2.1 Mathematical model** 269

270 **2.1.1 Model overview** 271

272 We constructed a seven-variable coupled system of partial differential equations de-
273 scribing resting and activated macrophages and microglia (M_R and M_A , respectively),
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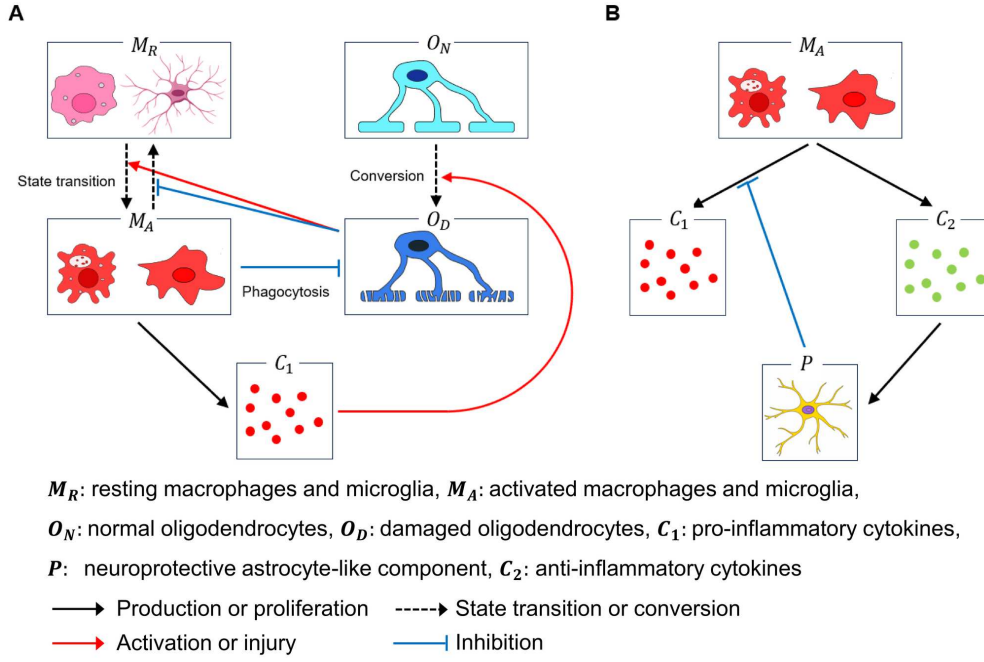


Figure 2 Schematic overview of the mathematical model. (A) Core lesion-forming pathway. **(B)** Suppressive pathway mediated by anti-inflammatory cytokines and a neuroprotective astrocyte-like component. For clarity, degradation and other auxiliary terms are omitted. The complete equations and the biological interpretation of individual terms are provided in Additional file 1.

normal and damaged oligodendrocytes (O_N and O_D , respectively), pro-inflammatory and anti-inflammatory cytokines (C_1 and C_2 , respectively), and a neuroprotective astrocyte-like component (P). All state variables were treated as continuous functions of time t and spatial position (x, y) in a two-dimensional domain $\Omega \subset \mathbb{R}^2$. Diffusion terms were included only for variables assumed to spread spatially. The model structure, including the core lesion-forming and suppressive pathways, is summarized schematically in Fig. 2. The complete governing equations and the biological interpretation of each model term are provided in Additional file 1.

To facilitate comparison with Klüver–Barrera (KB) myelin staining, we used $O_D + O_N$ as a coarse proxy for myelin staining intensity, assuming that the local myelin signal scales with the summed areal density of the oligodendrocyte-related variables in the model.

323 2.1.2 Core lesion-forming pathway

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325 The core lesion-forming pathway represented in Fig. 2A begins with a small central
326 focus of oligodendrocyte and myelin injury, which was prescribed as part of the initial
327 conditions rather than generated within the model. The detailed initial conditions are
328 provided in Additional file 1. Thus, the model does not address the initiating cause of
329 demyelination but describes how an established focus of tissue damage subsequently
330 expands and evolves.
331
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333 Within the initial lesion, damaged oligodendrocytes and associated myelin debris
334 activate resting macrophages and microglia (O_D -dependent $M_R \rightarrow M_A$) [24, 25].
335 Once activated, these cells produce pro-inflammatory cytokines ($M_A \rightarrow C_1$) [25, 26].
336 These mediators injure otherwise normal oligodendrocytes and promote their transi-
337 tion to a damaged state (C_1 -mediated $O_N \rightarrow O_D$) [25, 27]. Activated macrophages
338 and microglia subsequently phagocytose and remove damaged oligodendrocytes (M_A -
339 mediated clearance of O_D), thereby reducing the myelin content proxy ($O_D + O_N$)
340 [28–30]. Thus, activated macrophages and microglia both promote lesion expan-
341 sion through inflammatory mediator production and limit further damage-associated
342 activation through phagocytic clearance of damaged oligodendrocytes [31, 32].
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352 2.1.3 Suppressive pathway

353 In the suppressive pathway shown in Fig. 2B, activated macrophages and microglia are
354 not exclusively pro-inflammatory but can also produce anti-inflammatory cytokines,
355 such as IL-10 ($M_A \rightarrow C_2$) [32–34]. These cytokines can promote astrocyte-mediated
356 protective responses, represented in the model by the neuroprotective astrocyte-like
357 component ($C_2 \rightarrow P$) [35]. This astrocyte-mediated protective response can attenu-
358 ate microglial activation and pro-inflammatory cytokine expression. This regulatory
359 interaction is represented in the model as P -mediated inhibition of pro-inflammatory
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mediator production by activated macrophages and microglia (P -mediated inhibition of $M_A \rightarrow C_1$) [35]. Thus, this pathway forms a negative-feedback loop that counterbalances the lesion-promoting inflammatory pathway described in Fig. 2A.

2.1.4 Parameter settings and numerical simulation

Initial-condition values not directly constrained by experimental data are labeled as “Assumed” in Table S1, whereas model parameters without direct experimental constraints are labeled as “Estimated” in Table S2. Parameter values, units, and sources are listed in Table S2.

Initial conditions were specified as a radially symmetric top-hat seed with a radius of $r_0 = 0.5$ mm at the lesion center. This radially symmetric initialization was motivated by our previous three-dimensional MRI observation of an approximately spherical concentric demyelinating lesion in a patient with MS [36]. Accordingly, lesion evolution was represented as an outwardly propagating front arising from a localized core. Within the seed, the oligodendrocyte-related density was initialized as predominantly damaged, whereas outside the seed it was initialized as normal. Baseline values were anchored to reported densities of macrophages and microglia and myelin-related oligodendrocyte density [37, 38].

Simulations were performed on a 40×40 mm Cartesian domain with $\Delta x = \Delta y = 0.05$ mm. Diffusion terms were solved using an alternating-direction implicit scheme with Neumann boundary conditions, whereas reaction terms were advanced using an explicit Euler method with $\Delta t = 0.2$ min [39]. For computational efficiency, the implementation exploited symmetry about the lesion center, but all results are reported in the original full-domain coordinates.

2.1.5 Lesion-pattern classification and sensitivity analysis

The BCS pattern was defined by the presence of at least two local maxima and two local minima in the myelin content proxy profile [8, 40], with a maximum difference

415 between adjacent extrema $\Delta_{\max} \geq 20$ cells/mm², corresponding to 5% of the baseline
416 myelin level. This value was selected as an operational threshold informed by the mag-
417 nitude of differences in oligodendroglial density estimated from previous pathological
418 data [41].
419

421 The myelin content proxy was analyzed along the center-crossing transect at $y =$
422 20 mm, and the radial distance from the lesion center was defined as $s = x - 20$
423 for $x \geq 20$ mm. Because the simulations were initialized radially symmetrically with
424 spatially homogeneous and isotropic coefficients, this fixed transect was used as a
425 reproducible one-dimensional summary. Local extrema were detected in the region
426 $s \geq 5$ mm, and the outermost extremum was excluded to reduce boundary effects. The
427 lesion front was defined as the outermost radial position at which the myelin content
428 proxy returned to within 1 cell/mm² of the baseline value at $t = 10,000$ min. When
429 no recovery occurred before the domain boundary, the lesion diameter was treated as
430 domain-limited.
431

432 Assuming approximate radial symmetry, lesion diameter was estimated as $2s_{\text{front}}$.
433 Lesions with $\Delta_{\max} < 20$ were then classified according to their estimated diameter:
434 those with $2s_{\text{front}} > 20$ mm were classified as the TDL pattern, whereas those with
435 $2s_{\text{front}} \leq 20$ mm were classified as the MS pattern [42].
436

437 For one-at-a-time sensitivity analyses, selected parameters were varied from 0.01-
438 fold to 100-fold of their baseline values using a non-uniform grid enriched around the
439 baseline value. For the two-parameter sensitivity analysis, k_{22} and k_{31} were varied
440 simultaneously over the same range. Each simulation was classified as MS, BCS, or
441 TDL using the criteria described above.
442

454 2.1.6 Intervention analysis

455 Post-onset interventions were simulated by changing a single parameter at $t_{\text{int}} = 1,500$
456 or 5,700 min, corresponding to approximately 1 or 4 days after simulation onset,
457 respectively, and maintaining the modified value thereafter. All other parameters
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were held constant. Simulations were performed using parameter sets that generated the BCS and TDL patterns and were compared with the corresponding untreated simulations. Final lesion diameter at $t = 10,000$ min was used as the outcome measure because it provided a common quantitative measure of lesion expansion across intervention conditions.

2.2 Pathology analysis

2.2.1 Materials and ethics statement

We analyzed archival autopsy brain tissue from three Filipino patients with pathologically confirmed BCS, each with concentric demyelinating lesions, and one Japanese patient with pathologically confirmed MS. The three patients with BCS were women aged 23, 40, and 43 years, respectively, at the time of autopsy, and the patient with MS was a 55-year-old man. The autopsy specimens were fixed in 10% neutral buffered formalin and processed into paraffin-embedded sections. The sections underwent routine hematoxylin and eosin staining and KB staining. Selected sections were also subjected to CD68 immunohistochemistry to qualitatively assess the distribution of macrophages and microglia. Representative CD68-stained sections are shown in Fig. 1.

The MRI/clinical and neuropathological components were approved separately by the Kyushu University institutional review board (IRB) for Clinical Research (Nos. 575 and 25210, respectively). Written informed consent was obtained for the MRI/clinical component, whereas an opt-out approach was used for the archival autopsy tissue in accordance with institutional policy. Representative fluid-attenuated inversion recovery (FLAIR) images from one patient with MS, one with BCS, and one with a TDL were selected from the MRI/clinical dataset to illustrate the characteristic lesion morphologies shown in Fig. 1. The diagnoses of these patients were established on the basis of clinical and radiological assessments by neurologists. The MRI/clinical

507 and neuropathological datasets were analyzed independently without individual-level
508 linkage.
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511 **2.2.2 Image analysis**

512

513 For pathological image analysis, we developed a custom pipeline implemented in
514 Python version 3.11.1, using OpenCV, NumPy, pandas, SciPy, scikit-image, and
515 Matplotlib [43–48].
516

517 Red–green–blue images were converted to grayscale, percentile-normalized after
518 excluding the lowest and highest 1% of pixel intensities, and inverted so that darker
519 KB staining corresponded to higher signal intensity. The center of each concentric
520 lesion was visually identified by two neurologists and used as the origin for radial
521 analysis. Any disagreements in center selection or extrema exclusion were resolved by
522 consensus.
523

524 Radial intensity profiles were summarized at 12 target angles separated by 30°
525 intervals. For each target angle, neighboring profiles within $\pm 2^\circ$ were pooled, and the
526 median intensity at each radial position was used as the representative sector profile.
527 Profiles were smoothed using a third-order Savitzky–Golay (SG) filter [49] with a
528 window width of 0.2 mm. Local extrema were detected automatically and then visually
529 reviewed by two neurologists to exclude artifacts and non-lesional extrema.
530

531 Six profile-derived metrics were quantified: layer thickness, defined as the radial
532 distance between consecutive maxima; adjacent-extrema intensity difference, defined
533 as the vertical difference between a maximum and neighboring minima; radial trends
534 in layer thickness, maxima, and minima, estimated by linear regression against radius;
535 and slope difference, defined for each minimum–maximum–minimum triplet as the
536 absolute outer slope minus the absolute inner slope.
537

538 For analysis of the mathematical model, the same radial framework was applied to
539 the myelin content proxy ($O_D + O_N$). For comparison with the normalized pathologi-
540 cal intensity profiles, the model-derived $O_D + O_N$ profiles were divided by the baseline
541

value of 400. Percentile-based normalization and SG filtering were not applied to the model output because the simulated profiles were not affected by staining variability or image-acquisition artifacts. To avoid instability related to the lesion core, the central region within 5 mm of the origin was excluded from the analysis. The same definitions of layer thickness, adjacent-extrema intensity difference, radial trends in layer thickness, maxima, and minima, and slope difference were applied to the resulting radial profiles.

2.2.3 Statistical analysis

Continuous variables derived from the radial profiles are presented as the median and interquartile range. The prespecified hypotheses of positive radial trends in layer thickness, maxima, and minima, as well as positive outer-minus-inner slope differences, were tested using one-sided Wilcoxon signed-rank tests. For each metric, the three p values obtained from Cases 1–3 were adjusted for multiple comparisons using the Holm method. A Holm-adjusted $p < 0.05$ was considered statistically significant. All analyses were performed using Python version 3.11.1 with NumPy, pandas, SciPy, and Matplotlib [44–46, 48]. The observation-level data, summary statistics, and hypothesis-test results underlying the quantitative layer-metric analyses are provided in Additional file 2.

599 3 Results

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602 3.1 Model simulations support a shared mechanistic spectrum

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604 across MS, BCS, and TDLs

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606 3.1.1 A unified model generates distinct MS, BCS, and TDL

607

608 patterns

609

610 Using the same governing equations and initial lesion configuration but different values
611 of k_{22} , the model generated three distinct lesion morphologies (Fig. 3). The MS pattern
612 remained small and spatially confined, the BCS pattern developed repeated alternat-
613 ing concentric bands of higher and lower myelin content proxy values, and the TDL
614 pattern expanded broadly with little internal layering. These simulated morphologies
615 qualitatively resembled the corresponding MRI findings of MS, BCS, and TDL. Thus,
616 a single model framework reproduced distinct lesion patterns corresponding to the
617 three disorders.
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624 3.1.2 Oligodendrocyte vulnerability and the inflammatory activity

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626 of macrophages and microglia drive lesion-pattern transitions

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628 Guided by our a priori hypothesis, we varied oligodendrocyte vulnerability (k_{22}) and
629 the inflammatory activity of macrophages and microglia (k_{31}) while retaining the
630 same governing equations and initial lesion configuration. Increasing either parameter
631 shifted lesion morphology from a small MS pattern through a concentric BCS pattern
632 to a broadly expanding TDL pattern (Fig. 4A,B).
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635 To quantify these transitions and extend the analysis to other parameters, le-
636 sions were classified using the predefined $\Delta_{\max}$ - and diameter-based criteria (Methods;
637 Fig. 4C). Single-parameter analyses confirmed clear monotonic transitions for both
638 k_{22} and k_{31} (Fig. 4D,E). At the highest tested k_{31} value, a residual lamellar feature
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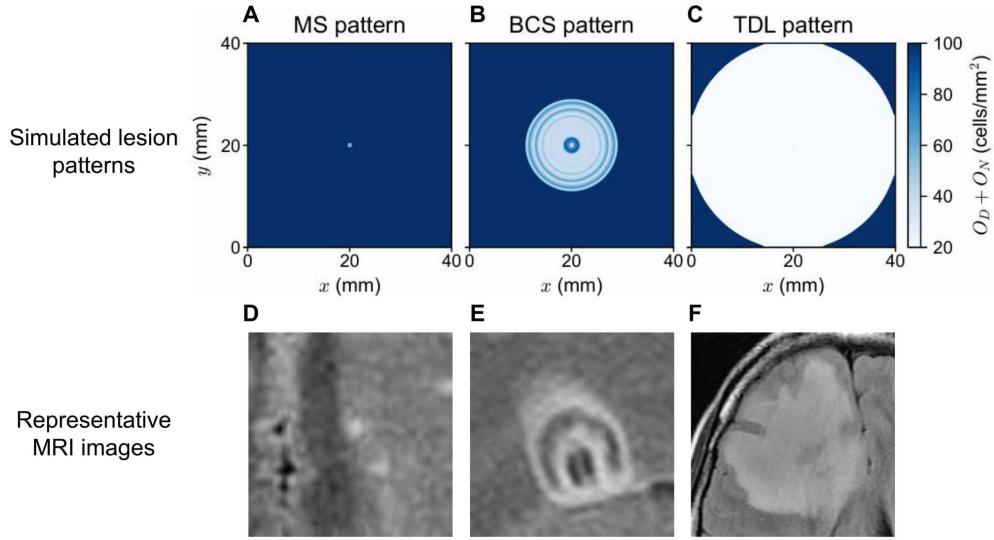


Figure 3 Multiple sclerosis, Baló's concentric sclerosis, and tumefactive demyelinating lesion patterns emerge from a unified model. (A–C) Simulated distributions of the myelin content proxy ($O_D + O_N$) generated using the same governing equations and initial lesion configuration, with k_{22} set to 3.0×10^{-4} , 3.0×10^{-3} , and 2.0×10^{-2} for the multiple sclerosis (MS), Baló's concentric sclerosis (BCS), and tumefactive demyelinating lesion (TDL) patterns, respectively (shown at $t = 7,500$ min). All other parameters were held at their baseline values. Higher $O_D + O_N$ values were interpreted as greater myelin preservation. The color scale was limited to 20–100 cells/mm² for visualization. (D–F) Representative fluid-attenuated inversion recovery (FLAIR) images of MS, BCS, and TDL, respectively. Magnified crops of the corresponding images shown in Fig. 1A–C are presented for direct qualitative comparison with the simulated lesion patterns.

remained near the lesion core, but no second concentric layer formed. Accordingly, the lesion met the TDL criteria.

The two-parameter analysis showed the MS pattern at lower values, the TDL pattern at higher values, and the BCS pattern mainly in the intermediate region (Fig. S1). Broader parameter exploration showed similar monotonic transitions for k_{12} and C_0 , whereas the remaining parameters had limited or non-monotonic effects (Fig. S2). Because k_{12} and C_0 act within the same inflammatory and oligodendrocyte-injury pathways represented by k_{31} and k_{22} , respectively, subsequent analyses focused on k_{22} and k_{31} as representative control axes. These findings indicate that variations in oligodendrocyte vulnerability and the inflammatory activity of macrophages and microglia drive transitions among the MS, BCS, and TDL patterns in the model.

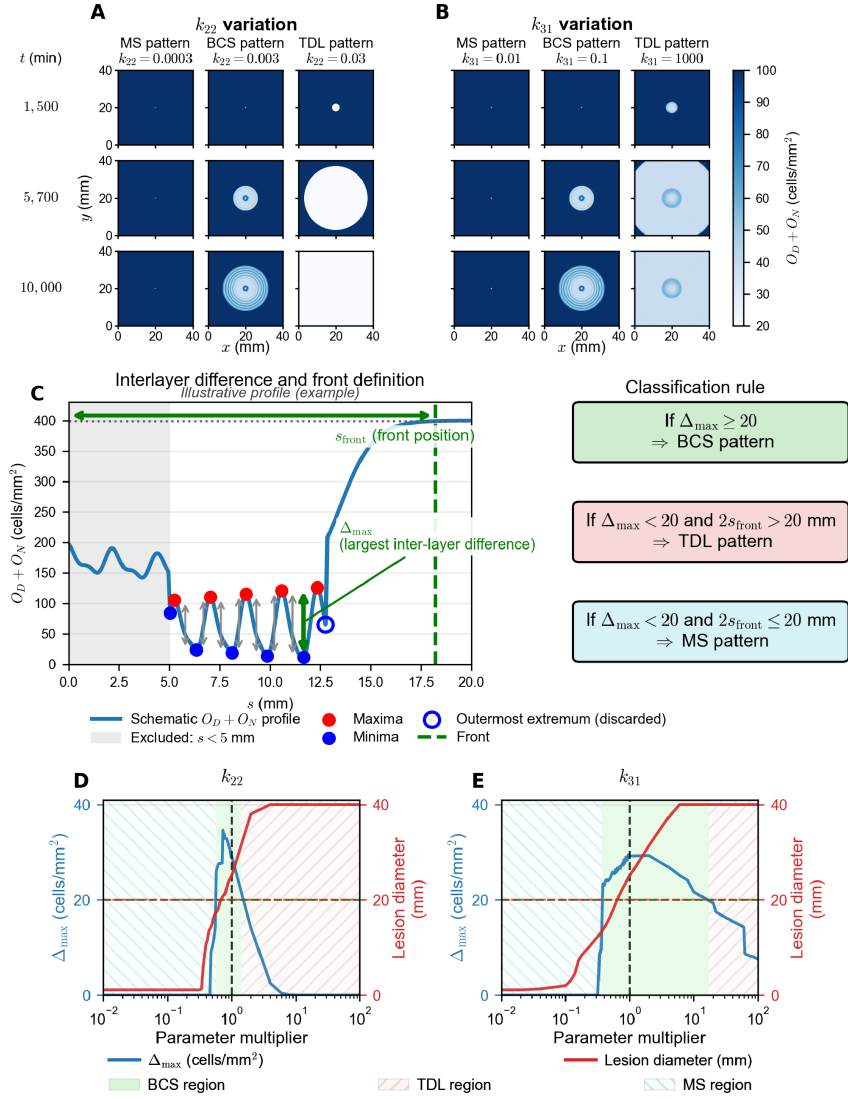


Figure 4 Parameter-dependent transitions among multiple sclerosis, Baló's concentric sclerosis, and tumefactive demyelinating lesion patterns. (A, B) Temporal evolution of $O_D + O_N$ at $t = 1,500, 5,700,$ and $10,000$ min for selected k_{22} and k_{31} values, respectively. The color scale was limited to $20\text{--}100$ cells/mm² for visualization. The highest k_{31} value in (B) lies outside the range shown in (E). (C) Definition of the maximum interlayer difference, $\Delta_{\max}$, and lesion-front position, s_{front} , together with the lesion-pattern classification rules. The variable s denotes the radial distance from the lesion center along the analyzed half-transect, and $O_D + O_N$ represents the myelin content proxy. Lesions were classified as the Baló's concentric sclerosis (BCS) pattern when $\Delta_{\max} \geq 20$ cells/mm², the tumefactive demyelinating lesion (TDL) pattern when $\Delta_{\max} < 20$ cells/mm² and $2s_{\text{front}} > 20$ mm, and the multiple sclerosis (MS) pattern when $\Delta_{\max} < 20$ cells/mm² and $2s_{\text{front}} \leq 20$ mm. (D, E) Single-parameter sensitivity analyses of k_{22} (oligodendrocyte vulnerability) and k_{31} (the inflammatory activity of macrophages and microglia), respectively. The blue and red curves show $\Delta_{\max}$ and lesion diameter, respectively. Horizontal and vertical dashed lines indicate the classification thresholds and reference parameter values, respectively.

3.2 Histopathology and model simulations show similar spatial features	737
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3.2.1 Activated macrophages and microglia localize to the lesion edge in both histopathology and simulations	741
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Using the baseline parameter values and initial conditions, the model generated a BCS pattern (Figs. 5 and S3, Supplementary Movies 1 and 2, provided as Additional files 3 and 4). During lesion evolution, alternating bands of higher and lower myelin content proxy values ($O_D + O_N$) emerged and propagated outward, while activated macrophages and microglia (M_A) remained sharply localized near the advancing lesion front. Spatiotemporal kymographs further showed a narrow outward-moving M_A peak at the lesion front, accompanied by the successive formation of alternating $O_D + O_N$ bands behind the front (Fig. S4). Thus, the simulated localization of activated macrophages and microglia at the advancing lesion front was consistent with the pathological finding that these cells accumulate at the lesion edge.	745
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3.2.2 Simulated demyelination profiles resemble those observed in histopathology	763
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We next compared the simulated BCS pattern with radial profiles derived from KB-stained sections from three BCS cases and one MS reference lesion. Alternating demyelinated and relatively myelin-preserved layers were observed in all three BCS lesions but not in the MS reference lesion (Figs. 6A and S5).	767
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Layer thickness was similar between pathology and the model, whereas the model showed smaller adjacent-extrema intensity differences than the pathological lesions (Fig. 6C and Table S3).	773
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Both pathology and the model showed minimal radial variation in layer thickness, a more pronounced outward increase in maxima than in minima, and boundary asymmetry characterized by steeper outer slopes than inner slopes. In the pathological	779
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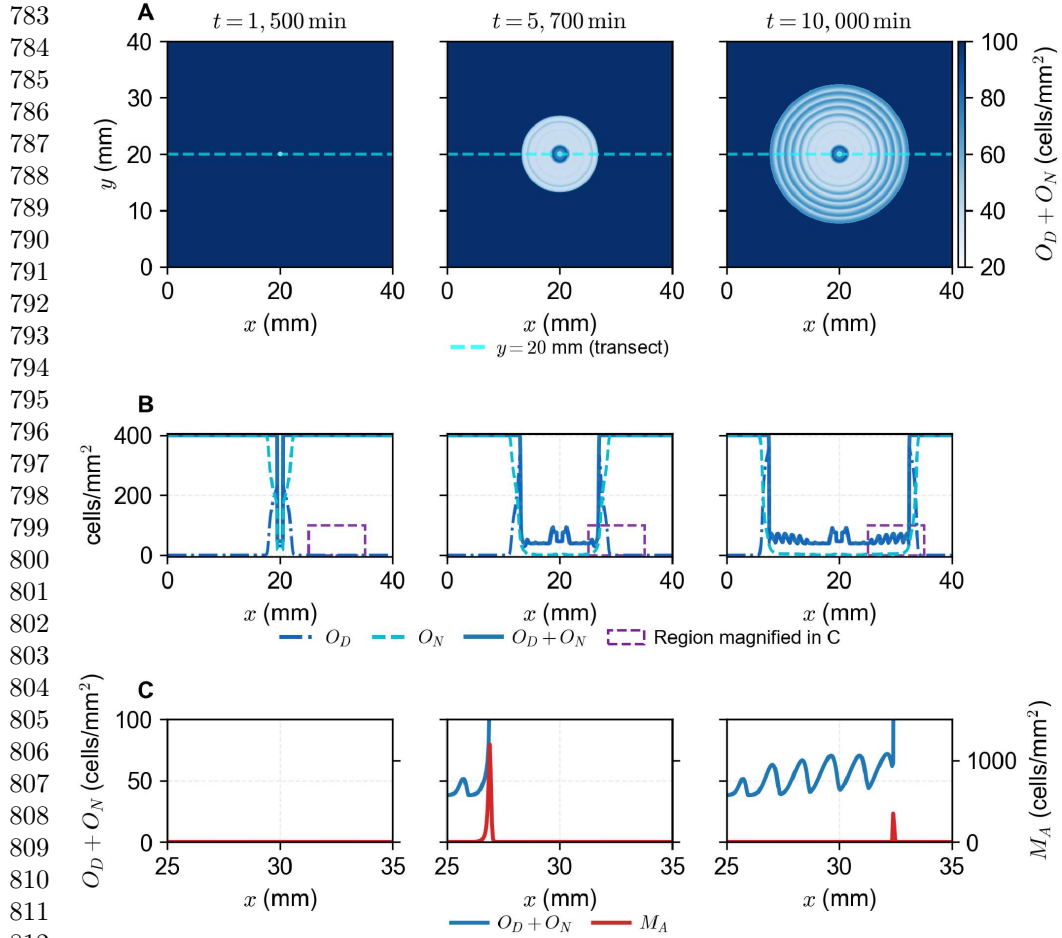


Figure 5 Model simulation of Baló's concentric sclerosis pattern evolution. (A) Two-dimensional maps of $O_D + O_N$, used as a myelin content proxy, at $t = 1,500$, $5,700$, and $10,000$ min, corresponding approximately to 1, 4, and 7 days, respectively. Blue indicates higher values, whereas white indicates lower values. The cyan dashed line indicates the horizontal transect at $y = 20$ mm used for the one-dimensional profiles. For visualization, the color scale is limited to 20–100 cells/mm². (B) Profiles of damaged and normal oligodendrocytes (O_D and O_N , respectively) and their sum ($O_D + O_N$) along the $y = 20$ mm transect. The purple dashed rectangles indicate the regions magnified in (C). (C) Magnified profiles over $x = 25$ – 35 mm, showing $O_D + O_N$ on the left axis and activated macrophages and microglia (M_A) on the right axis.

specimens, after Holm correction, significant radial trends remained only for maxima in Case 1 and minima in Case 3, whereas boundary asymmetry remained significant in all three cases. Radial trends in layer thickness were not significant in any case (Fig. 6C and Table S4).

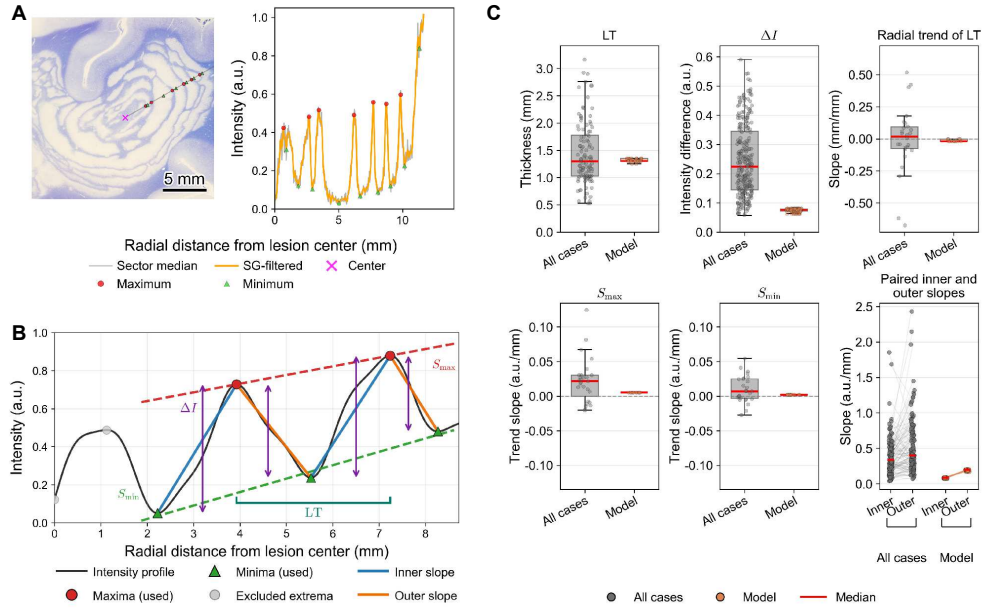


Figure 6 Quantitative analysis of concentric-layer structure in pathological Baló's concentric sclerosis (BCS) lesions and the model. (A) Representative Klüver-Barrera-stained section and its radial intensity profile. The magenta cross indicates the lesion center, and red circles and green triangles indicate selected local maxima and minima, respectively. The orange line shows the Savitzky-Golay-filtered profile. (B) Definitions of layer thickness, adjacent-extrema intensity difference (ΔI), radial trends in maxima and minima, and paired inner and outer boundary slopes. (C) Comparison of layer thickness, adjacent-extrema intensity difference, radial trends in layer thickness, maxima, and minima, and paired inner and outer boundary slopes between pooled pathological observations from three BCS cases and the simulated BCS pattern. Gray and orange symbols indicate pathological observations and model results, respectively; red lines indicate medians. The "All cases" group excludes the multiple sclerosis reference lesion. LT , layer thickness; ΔI , adjacent-extrema intensity difference; S_{max} and S_{min} , radial trends of local maxima and minima, respectively; a.u., arbitrary units.

Despite underestimating interlayer contrast, the model reproduced the other major spatial features observed in the pathological lesions, including layer thickness, radial trends, and boundary-slope asymmetry, showing overall similarity to the pathological demyelination profiles.

875 3.3 Simulations identify potential therapeutic strategies for

876 BCS and TDLs

878 879 3.3.1 Earlier therapeutic intervention more effectively suppresses 880 lesion progression

883 We first examined a fivefold increase in k_{41} , the induction rate of the neuroprotective
884 astrocyte-like component P by anti-inflammatory cytokines C_2 , while keeping all other
885 parameters fixed. This intervention reduced final lesion diameter under both BCS and
886 TDL pattern conditions, with greater suppression after early intervention than after
887 delayed intervention (Fig. 7A).

891 892 3.3.2 Enhancement of protective and anti-inflammatory pathways 893 suppresses lesion expansion

896 We then performed single-parameter intervention analyses for four mechanistically
897 selected parameters: k_{22} , k_{31} , k_{41} , and k_{51} . For k_{22} and k_{31} , the interventions were
898 modeled as reductions in oligodendrocyte vulnerability and in the inflammatory ac-
899 tivity of macrophages and microglia, respectively. For k_{41} and k_{51} , the interventions
900 were modeled as enhancements of the neuroprotective astrocyte-like pathway and
901 anti-inflammatory cytokine production, respectively (Fig. 7B).

906 Enhancement of protective or anti-inflammatory pathways (k_{41} and k_{51}) produced
907 stronger suppression of lesion expansion than moderate reductions of lesion-promoting
908 parameters (k_{22} and k_{31}) (Fig. 7B). In particular, approximately threefold increases
909 in k_{41} or k_{51} markedly reduced final lesion diameter, whereas achieving substantial
910 suppression by reducing k_{22} or k_{31} required reductions to approximately 20% of their
911 baseline values.

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Additional intervention analyses targeting k_{12} , C_0 , k_{13} , k_{14} , k_{21} , and P_0 are shown in Fig. S6. These simulations suggest that lesion progression can be substantially modified after the onset of lesion formation by strengthening protective or anti-inflammatory pathways.

4 Discussion

In this study, we developed a seven-variable model that generated a BCS pattern and reproduced several quantitative features of pathological BCS lesions. Under different parameter settings, the same framework also generated small, spatially confined MS patterns and broadly expanding TDL patterns, supporting the possibility that these lesion morphologies represent different manifestations of partially shared inflammatory demyelinating mechanisms. The intervention analyses further suggested that enhancing suppressive or protective pathways may limit acute lesion expansion.

4.1 Intuitive explanation of concentric ring pattern formation

In the model, a localized peak of activated macrophages and microglia (M_A) at the lesion margin produces pro-inflammatory cytokines (C_1), which convert adjacent normal oligodendrocytes (O_N) into a damaged state (O_D). Subsequent M_A -mediated clearance of O_D reduces the local myelin content proxy, $O_D + O_N$, leaving a demyelinated band behind the advancing activation front. As local O_D is depleted, damage-dependent activation of macrophages and microglia weakens, while the delayed C_2 - P suppressive pathway limits further C_1 production in previously affected tissue. Consequently, the dominant inflammatory activity shifts toward still-intact tissue farther outward. Repeated waxing and waning of this outwardly propagating activation pulse leaves alternating zones of greater and lesser myelin loss, forming concentric rings in the radially symmetric domain (Fig. S4). These dynamics resemble

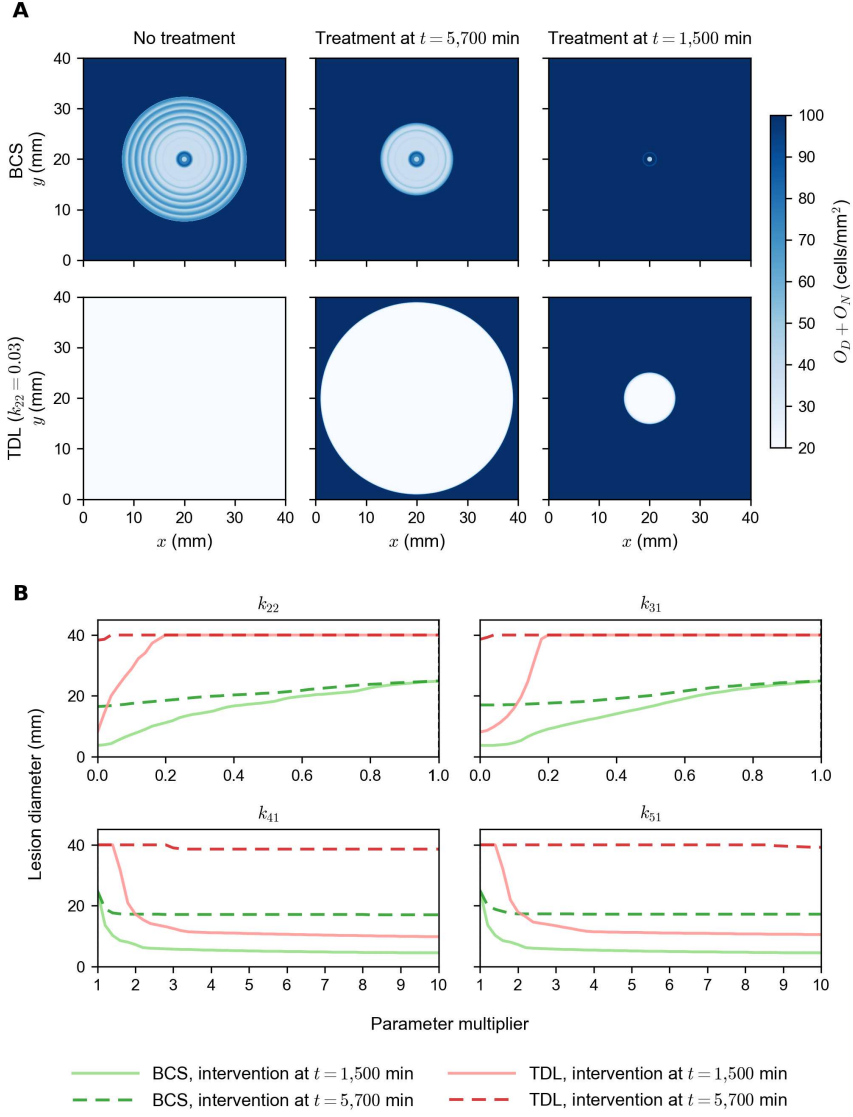


Figure 7 Single-parameter interventions in Baló's concentric sclerosis and tumefactive demyelinating lesion patterns. (A) Two-dimensional maps of the myelin content proxy $O_D + O_N$ at $t = 10,000$ min under no treatment, delayed treatment (initiated at $t = 5,700$ min), and early treatment (initiated at $t = 1,500$ min) for Baló's concentric sclerosis (BCS) (upper, $k_{22} = 0.0030$) and tumefactive demyelinating lesion (TDL) (lower, $k_{22} = 0.030$) patterns. The intervention was modeled as a fivefold increase in k_{41} , the induction parameter for the neuroprotective astrocyte-like component. (B) Final lesion diameter after parameter-specific interventions initiated at $t = 1,500$ or $t = 5,700$ min. Multipliers below 1 for k_{22} and k_{31} represent reductions in oligodendrocyte vulnerability and the inflammatory activity of macrophages and microglia, respectively. Multipliers above 1 for k_{41} and k_{51} represent enhancement of the neuroprotective astrocyte-like pathway and anti-inflammatory cytokine production, respectively. The solid lines indicate intervention at $t = 1,500$ min, and dashed lines indicate intervention at $t = 5,700$ min. Green and red lines indicate simulations starting from BCS and TDL patterns, respectively.

those described in reaction–diffusion models of concentric-ring formation in bacterial colonies [50, 51].

4.2 Comparison with previous mathematical models

Our model reproduced the spatial distribution of activated macrophages and microglia that contribute to demyelination. In previous models, macrophage and cytokine profiles showed multiple internal peaks that paralleled those of damaged oligodendrocytes, resulting in persistent activity within the lesion center [19–23]. These models attributed concentric pattern formation to Keller–Segel-type chemotaxis, in which macrophages migrate toward cytokine peaks, and to related pattern-forming instabilities. However, pathological studies have shown that in BCS, macrophages and microglia are most abundant at the outermost rim and are relatively sparse in the inner layers [12, 52]. In our model, by contrast, activated macrophages and microglia, together with pro-inflammatory cytokines, were concentrated near the advancing outer rim during concentric ring formation, more closely resembling the reported pathological findings.

A further important difference from previous models is that our model was compared with quantitative pathological radial profiles. Previous models were primarily assessed by whether they reproduced ring-like patterns of myelin content, whereas the present study also evaluated pathology-derived internal lamellar metrics, including boundary-slope asymmetry, radial intensity trends, and layer-scale measurements. Our approach provides a more comprehensive and objective comparison between the model and the pathological BCS lesions.

Although we do not exclude the possible contribution of chemotaxis, our model explores a complementary mechanism in which the BCS pattern can emerge from repeated transitions between resting and activated states of macrophages and microglia without explicitly incorporating chemotactic migration.

1059 4.3 Lesion spectrum based on oligodendrocyte vulnerability 1060 1061 and the inflammatory activity of macrophages and 1062 1063 microglia 1064

1065 Within the same model framework, distinct MS, BCS, and TDL patterns emerged un-
1066
1067 der different parameter conditions. Consistent with our a priori hypothesis, increasing
1068 either oligodendrocyte vulnerability (k_{22}) or the inflammatory activity of macrophages
1069
1070 and microglia (k_{31}) shifted lesion morphology from the MS pattern through the BCS
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1072 pattern to the broadly expanding TDL pattern, whereas decreasing either parame-
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1074 ter favored the MS pattern with limited lesion expansion. The BCS pattern emerged
1075 predominantly within an intermediate parameter regime between the MS and TDL
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1077 patterns (Fig. 8).

1078 Similar monotonic transitions were observed with k_{12} and C_0 , which affect other
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1080 steps in the inflammatory activation of macrophages and microglia and in inflam-
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1082 matory mediator-induced oligodendrocyte injury, respectively. These findings support
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1084 the interpretation of k_{22} and k_{31} as representative axes of broader oligodendrocyte-
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1086 injury and inflammatory processes, respectively, while other parameters may also
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1088 contribute to lesion morphology. By contrast, the remaining parameters had limited
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1090 effects on lesion-pattern classification or showed non-monotonic responses, indicating
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1092 that their effects on lesion morphology could not be summarized by simple monotonic
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1094 relationships.

1095 Oligodendrocyte vulnerability contributes to MS [4, 5], and BCS is associated with
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1097 pattern III, which features prominent oligodendrocyte apoptosis and degeneration
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1099 [9, 52]. TDLs are characterized by active, intense inflammatory demyelination with
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1101 prominent macrophage-rich infiltration [15, 53]. Although direct quantitative compar-
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1103 isons among MS, BCS, and TDLs are limited, our results suggest that the balance
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1105 between oligodendrocyte vulnerability and inflammatory activity may contribute to
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1107 shaping lesion morphology.

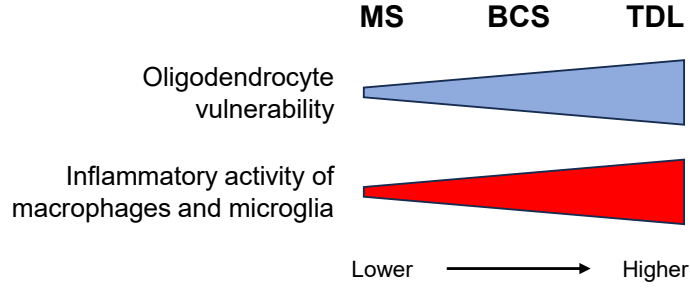


Figure 8 Schematic summary of the model-derived lesion spectrum. Multiple sclerosis (MS), Baló’s concentric sclerosis (BCS), and tumefactive demyelinating lesion (TDL) patterns are positioned along a conceptual spectrum derived from the model simulations. The blue and red arrows indicate progressive increases in oligodendrocyte vulnerability and the inflammatory activity of macrophages and microglia, respectively.

4.4 Therapeutic implications

In the intervention analysis, increasing parameters representing protective or anti-inflammatory processes reduced the final lesion diameter compared with the no-treatment condition in both BCS and TDL simulations. Earlier intervention was associated with a greater reduction in final lesion size.

BCS and TDLs are typically treated initially with high-dose corticosteroids, with plasma exchange used for steroid-refractory cases [8, 42, 54, 55]. However, evidence for the efficacy of these treatments remains limited because both conditions are rare and heterogeneous.

Because the present model did not simulate specific clinical treatments, these results should not be interpreted as directly predicting treatment efficacy or superiority over direct anti-inflammatory approaches. Rather, they suggest that the enhancement of suppressive or protective pathways may provide an additional mechanism for limiting acute lesion growth. This possibility is consistent with experimental findings suggesting that astrocyte-related pathways can influence lesion evolution [35, 56, 57].

Qualitatively similar intervention responses were observed in the parameter sets generating the BCS and TDL patterns, suggesting that shared inflammatory and protective mechanisms may influence acute lesion behavior in both lesion patterns.

1151 These findings require further validation, but they are consistent with the idea that
1152 both the inflammatory activity of macrophages and microglia and protective pathways
1153 contribute to acute lesion progression.
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1155

1157 4.5 Limitations and future directions

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1159 This study has several limitations.

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1161 First, the initial central focus of oligodendrocyte and myelin injury was prescribed
1162 as an initial condition rather than generated endogenously. The model therefore de-
1163 scribes the expansion and spatial evolution of an established lesion but does not
1164 address the initiating events that give rise to the initial focus of tissue injury.
1165

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1167 Second, the pathological image analysis was limited to three BCS cases, and patho-
1168 logical TDL specimens were unavailable. In particular, the TDL simulations should
1169 be regarded as model-defined patterns rather than pathologically validated lesions.
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1172 Finally, quantitative discrepancies remained between the simulations and patholog-
1173 ical findings. The model underestimated interlayer contrast and did not fully reproduce
1174 the morphology of the lesion core.
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1177 Larger pathological datasets incorporating additional immunohistochemical and
1178 spatial molecular analyses will be needed to validate and further refine the model.
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1182 5 Conclusions

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1185 A seven-variable reaction–diffusion model generated MS, BCS, and TDL patterns
1186 within a single framework and captured several quantitative spatial features ob-
1187 served in BCS pathology. These findings suggest that oligodendrocyte vulnerability
1188 and the inflammatory activity of macrophages and microglia may contribute to
1189 transitions among these lesion patterns within a shared mechanistic spectrum. Model-
1190 based intervention analyses further suggest that earlier intervention and enhancement
1191 of protective or anti-inflammatory pathways may suppress lesion progression. This
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framework may provide a useful perspective for interpreting BCS and TDLs in relation to MS and for guiding further validation using additional pathological and clinical data.

List of abbreviations

a.u.: arbitrary units

BCS: Baló's concentric sclerosis

FLAIR: fluid-attenuated inversion recovery

IRB: institutional review board

KB: Klüver–Barrera

MRI: magnetic resonance imaging

MS: multiple sclerosis

SG: Savitzky–Golay

TDL: tumefactive demyelinating lesion

Declarations

Ethics approval and consent to participate

This study comprised two independent components that were reviewed separately.

For the MRI/clinical component, the analysis of MRI images and associated clinical information was approved by the Kyushu University IRB for Clinical Research (No. 575), and written informed consent was obtained from all participants. For the neuropathological component, the analysis of archival autopsy tissue and digitized histopathological images was approved by the Kyushu University IRB for Clinical Research (No. 25210). An opt-out approach was used for the neuropathological

1243 component in accordance with institutional policy. All methods were carried out in ac-
1244 cordance with relevant guidelines and regulations, and the MRI/clinical and pathology
1245 datasets were analyzed independently without individual-level linkage.
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1249 **Consent for publication**

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1251 Written informed consent for publication was obtained from all participants in the
1252 MRI/clinical component. The histopathological images were derived from archived
1253 autopsy tissue analyzed under an institutional review board-approved opt-out protocol
1254 and contain no individually identifiable information.
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1259 **Availability of data and materials**

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1261 The numerical data underlying the quantitative pathological analyses are provided in
1262 Additional file 2. The simulation code and additional datasets are available from the
1263 corresponding author upon reasonable request.
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1267 **Competing interests**

1268

1269 The authors declare that they have no competing interests related to this work. Un-
1270 related to the present work, KM received honoraria from Alexion, Biogen, Chugai,
1271 Novartis, and Mitsubishi Tanabe. NI received honoraria from Alexion, Biogen, Chugai,
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1274 authors declare no competing interests.
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1281

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Authors' contributions	1289
	1290
KI conceived the study, developed the mathematical model, performed the patholog-	1291
ical image analysis, conducted the simulations, sensitivity analyses, and intervention	1292
analyses, and drafted the manuscript. KS contributed to the study design and	1293
manuscript structure and provided key input on the model framework and image-	1294
analysis methodology. KM, YK, and ET contributed to the manuscript structure	1295
and the interpretation of neuropathological image-analysis results. NM and RW con-	1296
tributed to the development and implementation of the mathematical model and the	1297
interpretation of the simulation results. TI, YO, and TT contributed to the manuscript	1298
structure and the interpretation of neuropathological image-analysis results. T. Ma-	1299
suda contributed to the manuscript structure. MN contributed to the manuscript	1300
structure and provided input on mathematical modeling. NI and T. Miura supervised	1301
the study and provided overall guidance for the project. All authors reviewed the	1302
manuscript and approved the final version.	1303
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Authors' information	1321
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Not applicable.	1323
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Additional files	1326
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Additional file 1 (.pdf): Supplementary Model Equations, Tables, and	1329
Figures. Complete model equations, biological interpretation of model terms, initial	1330
conditions, parameter values, supplementary sensitivity analyses, pathological profile	1331
figures, and additional intervention analyses.	1332
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Additional file 2 (.xlsx): Underlying numerical data for quantitative layer-metric analyses. Excel workbook containing observation-level data, summary statistics corresponding to Table S3, and hypothesis-test results corresponding to Table S4.

Additional file 3 (.mp4): Supplementary Movie 1. Time evolution of the simulated BCS pattern shown as two-dimensional maps of the myelin content proxy ($O_D + O_N$) from $t = 0$ to 10,000 min. The movie illustrates outward lesion expansion and the progressive formation of alternating concentric rings of higher and lower myelin content proxy values. For visualization, the color scale is limited to 20–100 cells/mm², with values above 100 cells/mm² shown as saturated.

Additional file 4 (.mp4): Supplementary Movie 2. Time evolution of one-dimensional profiles along the center-crossing transect during simulated BCS pattern formation from $t = 0$ to 10,000 min. The panels show, respectively, full-domain profiles of the myelin content proxy ($O_D + O_N$), damaged oligodendrocytes (O_D), and normal oligodendrocytes (O_N); a magnified view over $x = 25$ –35 mm showing the myelin content proxy and activated macrophages and microglia (M_A); profiles of resting macrophages and microglia (M_R), M_A , and the neuroprotective astrocyte-like component (P); and profiles of pro-inflammatory and anti-inflammatory cytokines (C_1 and C_2).

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