HOKKAIDO UNIVERSITY

Title	Membranous nephropathy preceding Bing-Neel syndrome: successful treatment with tirabrutinib
Author(s)	Watanabe-Kusunoki, Kanako; Nakazawa, Daigo; Ohigashi, Hiroyuki et al.
Citation	Journal of nephrology, 38(9), 2991-2996 https://doi.org/10.1007/s40620-025-02401-7
Issue Date	2025-09-26
Doc URL	https://hdl.handle.net/2115/98145
Rights	This version of the article has been accepted for publication, after peer review (when applicable) and is subject to Springer Nature's AM terms of use, but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: http://dx.doi.org/10.1007/s40620-025-02401-7
Type	journal article
File Information	Manuscript BNS MN TIN E9 20250719 J Nephrol Rev1_clean.pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Membranous Nephropathy Preceding Bing-Neel Syndrome: Successful Treatment with Tirabrutinib

Kanako Watanabe-Kusunoki[1], Daigo Nakazawa[1], Hiroyuki Ohigashi[2], Takahiro Tsuji[3], Tatsuya Atsumi[1]

1 Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan
2 Department of Hematology, Hokkaido University Faculty of Medicine and Graduate School of Medicine, Sapporo, Japan
3 Department of Pathology, Sapporo City General Hospital, Sapporo, Japan

Corresponding author
Kanako Watanabe-Kusunoki
Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University
Kita 14, Nishi 5, Kita-ku, Sapporo, 060-8648, Japan

Phone: +81-11-706-5915
Fax: +81-11-706-7710

Abstract word count: 194
Text word count: 912
Figures: 2
Tables: 0
References: 9

Abstract:

We report a unique case of membranous nephropathy and tubulointerstitial nephritis preceding neurological manifestations of Bing-Neel syndrome (BNS), a rare variant of Waldenström macroglobulinemia. A 46-year-old man presented with nephrotic syndrome, and kidney biopsy revealed membranous nephropathy with phospholipase A2 receptor positivity and IgG4 predominance. Despite initial partial remission with corticosteroids and cyclosporine, neurological symptoms emerged alongside nephrotic syndrome relapse two years after onset. Diagnostic workup revealed serum monoclonal IgM kappa, abnormal lymphoplasmacytic cells in bone marrow and cerebrospinal fluid, and *MYD88* L265P mutation in the latter, confirming BNS diagnosis. Immunostaining of the initial kidney biopsy demonstrated IgM-kappa-positive lymphoplasmacytic infiltration consistent with the monoclonal protein. After bendamustine-rituximab therapy showed partial effectiveness, tirabrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, achieved complete remission of both renal and neurological manifestations with sustained response over three years. Immunofluorescence staining revealed increased NF-κB and STAT3 expression in infiltrating immune cells and elevated NF-κB in surrounding tubular epithelial cells, suggesting activation of these pathways downstream of the *MYD88* mutation in kidney pathology. Our findings suggest a potential contribution of BTK signaling to both kidney and neurological pathology in BNS, with tirabrutinib achieving clinical improvement in both organ manifestations.

Keywords:

Bing-Neel syndrome, Membranous nephropathy, Tirabrutinib, Waldenström macroglobulinemia

Introduction

Bing-Neel syndrome (BNS) is a rare variant of Waldenström macroglobulinemia (WM), an IgM-secreting lymphoplasmacytic lymphoma that can affect multiple organ systems. BNS is characterized by the infiltration of malignant lymphoplasmacytic cells into the central nervous system, leading to diverse neurological manifestations, including paresis, cognitive changes and other neurological disorders.(1)

The concurrent presentation of BNS with kidney disease has not been reported. However, kidney involvement occurs in approximately 4.2% of WM patients and typically presents in three patterns: amyloidosis, nonamyloid glomerulopathy (including cryoglobulinemic glomerulonephritis) and nonamyloid tubulointerstitial diseases (including cast nephropathy). These conditions involve monoclonal IgM or light chain deposits and/or malignant B-cell infiltration.(2) Membranous nephropathy is a rare presentation of WM-related kidney disease.

Treatment outcomes for WM-related kidney disease vary, with studies reporting mortality rates of 22-53% and progression to end-stage kidney disease in 5-37% of cases.(3) Here we report a unique case of refractory nephrotic syndrome that preceded neurologic symptoms as a manifestation of BNS. A kidney biopsy revealed membranous nephropathy with tubulointerstitial nephritis, showing IgM kappa-positive lymphoplasmacytic cell infiltration in the kidney interstitium. Treatment with tirabrutinib, a second-generation Bruton’s tyrosine kinase (BTK) inhibitor, achieved parallel improvement in both kidney and neurologic manifestations, with sustained complete remission of nephrotic syndrome over 3 years of follow-up.

Case Presentation

A 46-year-old man presented with nephrotic syndrome in August 2017, manifesting severe proteinuria (8.7 g/gCr) and hypoalbuminemia (1.7 g/dL) with slight decrease in kidney function. Renal biopsy revealed capillary wall thickening, granular IgG deposition on capillaries with IgG4 subclass predominance, positive phospholipase A2 receptor (Figure 1A-1E), as well as tubulointerstitial nephritis with lymphoplasmacytic infiltration (Figure 1F). Initial workup for secondary causes was unremarkable, except for elevated IgM (859 mg/dL) without M spike in serum nor urine, and no detectable urine monoclonal proteins. The patient was diagnosed with primary membranous nephropathy with tubulointerstitial nephritis and treated with corticosteroids and cyclosporine, gradually achieving partial remission by February 2019 (proteinuria reduced to around 1 g/gCr) (Figure 2)

In October 2019, the patient experienced nephrotic syndrome relapse (proteinuria 4.9 g/gCr) with first neurological manifestations including hand tremor and urinary dysfunction. Despite corticosteroid pulse therapy for presumed inflammatory demyelinating disease based on neuroimaging findings (Figure 2), both renal and neurological symptoms persisted through corticosteroid tapering. Further evaluation in June 2020 revealed serum monoclonal IgM kappa and abnormal lymphoplasmacytic cells in both bone marrow and cerebrospinal fluid, with detection of *MYD88* L265P mutation in the latter, leading to a diagnosis of BNS. Immunostaining of the initial kidney biopsy demonstrated IgM-kappa-positive lymphoplasmacytic infiltration, consistent with the detected serum monoclonal protein (Figure 1G-1K).

Initial therapy with bendamustine-rituximab reduced urine protein levels while failed to achieve neurological disease control. In September 2020, treatment was switched to

tirabrutinib, which led to significant improvement in both renal and neurological symptoms. The patient has maintained remission for three years of follow-up (Figure 2).

Discussion

We report a case of refractory nephrotic syndrome preceding neurological symptoms in a patient with BNS. The patient was diagnosed with membranous nephropathy and tubulointerstitial nephritis based on kidney biopsy findings. Both manifestations were resistant to corticosteroid and cyclosporine therapy, but showed dramatic improvement with tirabrutinib, maintaining complete remission of nephrotic syndrome over 3 years.

Kidney biopsy revealed infiltration of IgM-kappa-positive lymphoplasmacytic cells in the interstitium, consistent with WM-related tubulointerstitial nephritis. The biopsy also demonstrated IgG deposition with IgG4 subclass predominance, while IgM staining was negative (data not shown). Additionally, phospholipase A2 receptor was positive in glomeruli, characteristic of primary membranous nephropathy. The association between membranous nephropathy and WM/BNS remains uncertain. Membranous nephropathy is rare in WM, reported in only 2% of cases without secondary causes.(4) In another study examining WM patients with kidney involvement, only two cases (3.5%) of membranous nephropathy were identified; however, one case showed atypical monoclonal IgG deposition for WM, while the other was complicated by amyloid glomerulopathy.(3) Furthermore, the absence of reported nephrotic syndrome cases specifically in BNS suggests the co-occurrence might be coincidental.

The *MYD88* L265P mutation, highly prevalent in WM, activates nuclear factor (NF)-κB signaling through BTK and Janus kinase/signal transducer and activator of

transcription (JAK-STAT) signaling pathways, together promoting lymphoplasmacytic cell survival.(5, 6) Notably, the *MYD88* L265P mutation is specifically associated with hematologic malignancies and is absent in nonhematologic tumors or solid metastatic tumors.(7) In our case, immunofluorescence staining revealed increased NF-κB and STAT3 expression in infiltrating immune cells and elevated NF-κB in surrounding tubular epithelial cells (Figure 1L). These findings suggest that malignant lymphoplasmacytic cells directly caused tubulointerstitial nephritis through activation of NF-κB and STAT3 signaling pathways downstream of the *MYD88* L265P mutation, leading to subsequent tubular inflammation and injury.(8)

The therapeutic response to tirabrutinib in both neurological and kidney manifestations suggests a potential role of BTK and its downstream NF-κB activation in these conditions in WM/BNS. Furthermore, the response of membranous nephropathy to tirabrutinib, despite resistance to corticosteroid and cyclosporine therapy, supports the potential benefit of B-cell targeted therapy, consistent with the effectiveness of rituximab in this condition.(9) However, we cannot exclude the possibility that the coexistence of membranous nephropathy and WM/BNS was coincidental, especially given that the response to tirabrutinib occurred after multiple prior therapies. Of note, while both pathological findings and epidemiological data support primary membranous nephropathy independent of WM/BNS, the remarkable response to tirabrutinib raises the possibility of a pathophysiological link between these conditions.

In conclusion, our case demonstrates BNS with membranous nephropathy and tubulointerstitial nephritis that preceded neurological symptoms and achieved complete remission with tirabrutinib. Our findings provide insights into the pathological mechanisms of WM-related tubulointerstitial nephritis through NF-κB and STAT3

149 signaling pathways downstream of *MYD88*-BTK in human tissue. BTK inhibition by
150 tirabrutinib resulted in clinical improvement of both kidney and neurological
151 manifestations, achieving sustained remission of nephrotic syndrome.

Declarations

Ethical approval

The Institutional Research Ethics Board does not require board review for a single case report when the patient's privacy is protected.

Informed consent to participate

The patients provided informed consent for publication of their case details and images.

Competing interests

The authors declare no competing financial interests.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding acknowledgement

This study received no funding.

Authors' Contributions

KW-K and DN conceptualized the case report, collected and analyzed case data. KW-K performed the literature search and drafted the manuscript. DN, HO, TT and TA critically reviewed and revised the manuscript. All the authors approved the final manuscript.

References

1. Ashruf OS, Mirzai S, George LL, Anwer F; Beyond monoclonal gammopathy of undetermined significance, clinical spectrum of immunoglobulin M gammopathy: a case series with focus on the diagnostic and management challenges. Int J Hematol Oncol 2023; 12(2):IJH44.

2. Chauvet S, Bridoux F, Ecotiere L, et al.; Kidney diseases associated with monoclonal immunoglobulin M-secreting B-cell lymphoproliferative disorders: a case series of 35 patients. Am J Kidney Dis 2015; 66(5):756-67.

3. Higgins L, Nasr SH, Said SM, et al.; Kidney Involvement of Patients with Waldenstrom Macroglobulinemia and Other IgM-Producing B Cell Lymphoproliferative Disorders. Clin J Am Soc Nephrol 2018; 13(7):1037-1046.

4. Vos JM, Gustine J, Rennke HG, et al.; Renal disease related to Waldenstrom macroglobulinaemia: incidence, pathology and clinical outcomes. Br J Haematol 2016; 175(4):623-630.

5. Yang G, Zhou Y, Liu X, et al.; A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenstrom macroglobulinemia. Blood 2013; 122(7):1222-32.

6. Ngo VN, Young RM, Schmitz R, et al.; Oncogenically active MYD88 mutations in human lymphoma. Nature 2011; 470(7332):115-9.

7. Alcoceba M, Garcia-Alvarez M, Medina A, et al.; MYD88 Mutations: Transforming the Landscape of IgM Monoclonal Gammopathies. Int J Mol Sci 2022; 23(10).

8. Marko L, Vigolo E, Hinze C, et al.; Tubular Epithelial NF-kappaB Activity Regulates Ischemic AKI. J Am Soc Nephrol 2016; 27(9):2658-69.

9. Fervenza FC, Appel GB, Barbour SJ, et al.; Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. N Engl J Med 2019; 381(1):36-46.

Figure Legends

Figure 1. Kidney biopsy findings

A)-E) Representative glomerular findings. (A) Periodic acid-methenamine silver (PAM) staining showing capillary wall thickening. (B) Immunofluorescence staining demonstrating IgG deposition. (C) IgG subclass staining. (D) Electron microscopy revealing subepithelial deposits and spike formation. (E) Immunohistochemical staining for phospholipase A2 receptor (PLA2R). Scale bars: 20 μm (A), 50 μm (B, C, E), 5 μm (D).

F)-K) Representative tubulointerstitial findings. (F) Hematoxylin and eosin (HE) staining. (G-K) Immunohistochemical staining for CD20 (G), CD138 (H), IgM (I), kappa (J), and lambda (K), demonstrating IgM-kappa-positive lymphoplasmacytic infiltration. Scale bars: 50 μm.

L) Immunofluorescence images of control tissue (healthy portion of renal cell carcinoma surgical specimen) and the present case. The present case shows increased expression of nuclear factor (NF)-κB (red) and signal transducer and activator of transcription 3 (STAT3) (green) in infiltrating immune cells, with elevated NF-κB in surrounding tubular epithelial cells. Nuclei were visualized with 4’,6-diamidino-2-phenylindole (DAPI, blue). Scale bars: 50 μm.

Figure 2. Clinical course

Alb: Albumin, BR: Bendamustine-rituximab, CsA: Cyclosporine, eGFR: Estimated glomerular filtration rate, IgM: Immunoglobulin M, mPSL: Methylprednisolone, MRI: Magnetic resonance imaging, PSL: Prednisolone.

Membranous Nephropathy Preceding Bing-Neel Syndrome: Successful Treatment with Tirabrutinib

Kanako Watanabe-Kusunoki[1], Daigo Nakazawa[1], Hiroyuki Ohigashi[2], Takahiro Tsuji[3], Tatsuya Atsumi[1]

1 Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan. 2 Department of Hematology, Hokkaido University Faculty of Medicine and Graduate School of Medicine, Sapporo, Japan. 3 Department of Pathology, Sapporo City General Hospital, Sapporo, Japan

Background

- Bing-Neel syndrome (BNS) is a rare variant of Waldenström macroglobulinemia (WM) with central nervous system involvement.
- Kidney involvement in WM occurs in 4.2% of cases, but membranous nephropathy (MN) is extremely rare.
- No previous reports of BNS with nephrotic syndrome.

Methods

- Single case report from Hokkaido University, Japan.
- 46-year-old man with nephrotic syndrome preceding neurological symptoms by 2 years
- Measures: Kidney biopsy with immunofluorescent NF-κB/STAT3 staining, cerebrospinal fluid analysis with *MYD88* L265P mutation detection.
- Ethical issues: Patient provided written informed consent for publication

Results

Tirabrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, was associated with complete remission of both MN and neurological symptoms for over 3 years (Figure A)

Strengths: Immunofluorescence revealed NF-κB and STAT3 activation in infiltrating lymphoplasmacytic cells and NF-κB in tubular cells, demonstrating potential MYD88-BTK pathway involvement in kidney pathology (Figure B).

Figure A

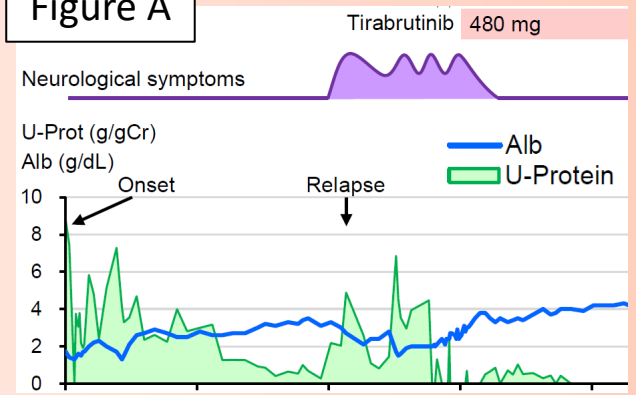
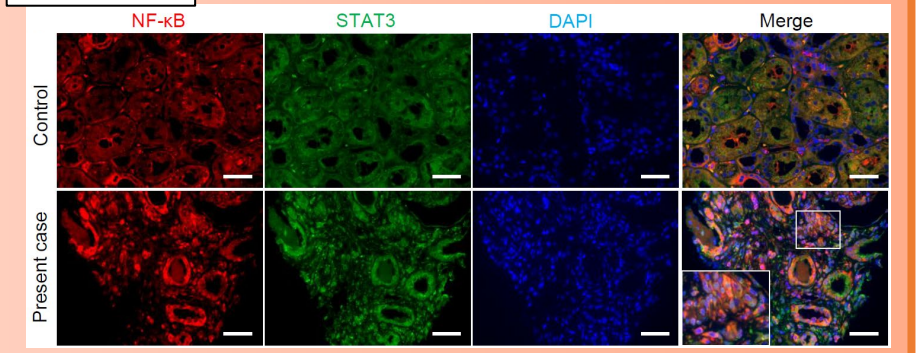


Figure B



Clinical applications: BTK inhibition improved both BNS and associated kidney disease.
Limits: Single case report.

Conclusions

First reported case of BNS with preceding MN and tubulointerstitial nephritis.
Immunofluorescence supports MYD88-BTK-NF-κB/STAT3 pathway in kidney pathology.
Tirabrutinib demonstrated clinical efficacy for both conditions in this case.

Journal of NEPHROLOGY
official journal of the Italian Society of Nephrology

Figure 1

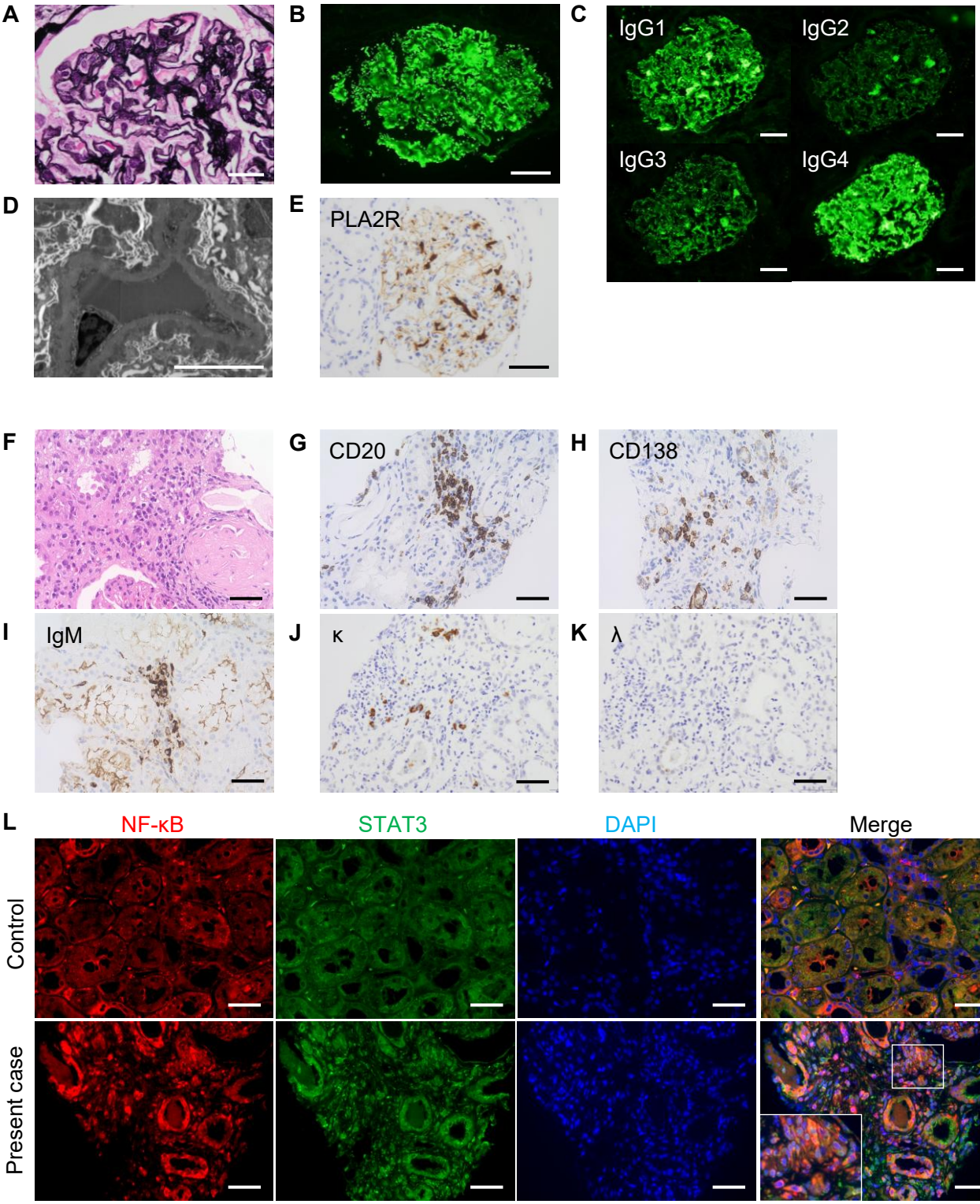
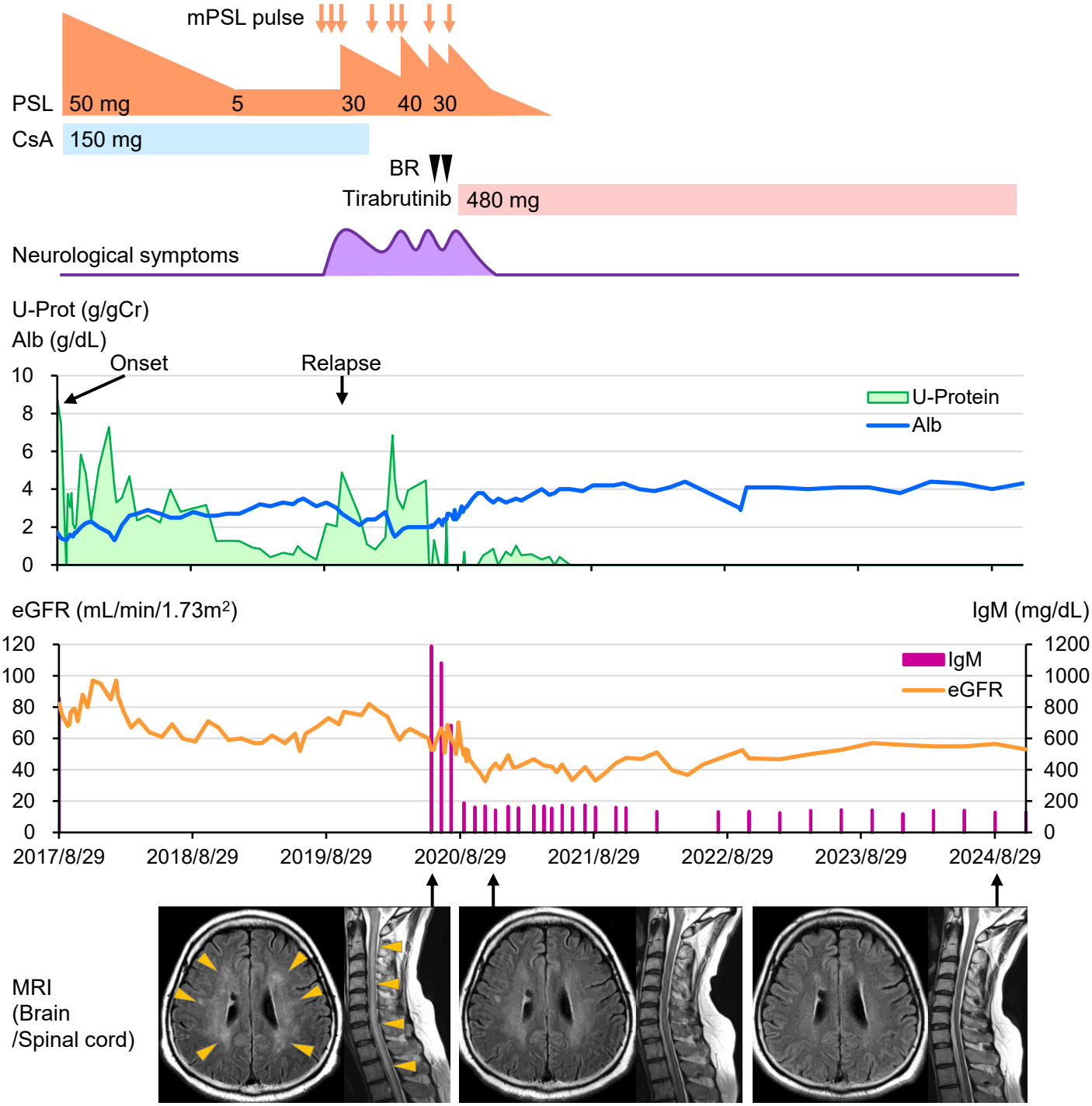

A
B
C
IgG1
IgG2
IgG3
IgG4
D
E
PLA2R
F
G
CD20
H
CD138
I
IgM
J
κ
K
λ
L
NF-κB
STAT3
DAPI
Merge
Control
Present case

Figure 2


mPSL pulse
PSL
50 mg
5
30
40
30
CsA
150 mg
BR
Tirabrutinib
480 mg
Neurological symptoms
U-Prot (g/gCr)
Alb (g/dL)
Onset
Relapse
U-Protein
Alb
eGFR (mL/min/1.73m²)
IgM (mg/dL)
IgM
eGFR
2017/8/29
2018/8/29
2019/8/29
2020/8/29
2021/8/29
2022/8/29
2023/8/29
2024/8/29
MRI
(Brain
/Spinal cord)