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Du, Steven

Fu, Dan

A Bota, Daniela

et al.

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CASE REPORT

Prolonged remission with ibrutinib maintenance therapy following radiation in a patient with relapsed primary CNS lymphoma

Steven Du[a,b], Dan Beverly Fu[b], Daniela A Bota[b,c] and Xiao-Tang Kong[*,b,c]

[a]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; [b]Department of Neurology, University of California Irvine, Irvine, CA 92868, USA; [c]Department of Neurological Surgery, University of California Irvine, Irvine, CA 92868, USA

ABSTRACT

Background: Treatment for refractory or relapsed primary CNS lymphoma (r/r PCNSL) is challenging. Salvage whole-brain radiation therapy (WBRT) is an option but has a short duration of disease control, so additional treatment modalities are warranted. **Case:** A 75-year-old female with r/r PCNSL who had multiple progressions after multiple lines of treatment underwent salvage WBRT. The patient received ibrutinib, a Bruton's tyrosine kinase inhibitor, as maintenance therapy for 18 months following WBRT with the intention of increasing survival duration after salvage WBRT. She survived 81 months from diagnosis, including 57 months after completion of WBRT. **Conclusion:** This case presentation describes the experience of using ibrutinib as maintenance therapy in treating r/r PCNSL after salvage WBRT.

Plain language summary: Treatment for refractory or relapsed primary CNS lymphoma (r/r PCNSL) is difficult. Salvage whole-brain radiation therapy (WBRT) is one treatment choice, but the effects do not last very long. Therefore, additional treatment regimens are needed. The authors report a 75-year-old female with r/r PCNSL who had several progressions after multiple lines of treatment and underwent salvage WBRT. Following WBRT, the patient received ibrutinib, a Bruton's tyrosine kinase inhibitor, as maintenance therapy for 18 months to increase the duration of survival after salvage WBRT. She survived 81 months from diagnosis, including 57 months after completion of WBRT. This case reflects the experience of using ibrutinib as maintenance therapy in treating r/r PCNSL after salvage WBRT.

TWEETABLE ABSTRACT

A 75-year-old female with relapsed primary CNS lymphoma had salvage whole-brain radiation therapy followed by ibrutinib maintenance therapy. She tolerated treatment and had prolonged survival. Further study of the effects of ibrutinib in this setting is suggested.

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1. Introduction

Primary CNS lymphoma (PCNSL) is a rare and aggressive subtype of non-Hodgkin's lymphoma that originates in lymphocytes and develops in the CNS, specifically the brain, spinal cord, eyes, or leptomeninges. PCNSL has an incidence rate of 0.5 per 100,000 persons per year, with 1500 new cases per year in the USA alone [1]. The outcomes of PCNSL are suboptimal. Left untreated, the median overall survival (OS) is approximately 1.5 months [2]. PCNSL symptoms, which include cognitive impairments, personality changes, focal neurological deficits, and seizures, can progress rapidly [3]. Biopsies are the gold standard for PCNSL diagnosis, while contrast-enhanced cranial MRI is often used for imaging diagnosis [4].

Standard induction therapy for PCNSL involves either single-agent high-dose methotrexate (HD-MTX) or HD-MTX-based combination therapy. Depending on physician preference, a variety of HD-MTX-based induction therapy regimens exist, such as single-agent HD-MTX, rituximab, methotrexate, and temozolomide (R-MT); rituximab, methotrexate, procarbazine, and vincristine (R-MPV); and methotrexate, cytarabine, thiotepa, and rituximab (MATRix) [5]. The introduction of HD-MTX-based regimens has greatly improved the prognosis of PCNSL in recent decades, achieving a complete or partial response in most patients with PCNSL and increas-

CONTACT Xiao-Tang Kong xkong@hs.uci.edu

ing the median OS from 12.5 months to 26 months [5,6].

Nonstandard consolidation therapy options for PCNSL include high-dose systemic chemotherapy with autologous stem-cell rescue; traditional chemotherapy such as cytarabine + thiotepa followed by carmustine + thiotepa, thiotepa, busulfan, and cyclophosphamide; high dose cytarabine + etoposide; and high-dose cytarabine [7] and half-dose whole-brain radiation therapy (WBRT) [8]. Nonstandard maintenance therapy options for PCNSL include monthly HD-MTX, temozolomide, rituximab, lenalidomide, procarbazine, and ibrutinib [7,9,10]. More attention has recently been drawn to maintenance therapy to prolong the duration of remission achieved by induction therapy, particularly in the elderly who cannot tolerate consolidation therapies [9].

Refractory or relapsed PCNSL (r/r PCNSL) is characterized by the disease being unresponsive to antilymphoma treatment or returning after completion of treatment. One-third of PCNSL cases are refractory to initial treatment, and nearly half of patients with PCNSL experience a relapse in disease within the first 2 years of diagnosis [11]. There are no standard therapies for r/r PCNSL. Nonstandard treatment regimens include rechallenging with single-agent HD-MTX or HD-MTX-based regimens, conventional chemotherapy, high-dose chemotherapy/autologous hematopoietic stem cell transplantation (HDC/ASCT), or WBRT [12–14]. WBRT is usually used as a last-line salvage therapy due to its neurotoxicity [14]. The duration of responses to salvage WBRT is often limited, as patients with r/r PCNSL who underwent salvage WBRT alone only survived for a median length of 10 to 16 months [15–18]. Therefore, additional maintenance therapy to extend survival after salvage WBRT for r/r PCNSL is warranted.

Ibrutinib is a Bruton's tyrosine kinase inhibitor that interferes with B-cell receptor signaling, hindering the survival of lymphoma cells. It is currently US FDA-approved to treat mantle cell lymphoma, chronic lymphocytic leukemia, and marginal zone lymphoma [19,20]. Ibrutinib can cross the blood–brain barrier. Single-agent ibrutinib has been used in clinical trials to treat patients with r/r PCNSL, showing good tolerance and survival benefits [21,22]. Because of its success in treating patients with r/r PCNSL, ibrutinib was applied as maintenance therapy following salvage WBRT for a patient who failed multiple treatment regimens, after carefully discussing the benefits and risks with the patient.

2. Case report

The patient, a 75-year-old (at diagnosis of CNSL) female, was diagnosed with PCNSL in early January 2016 after a biopsy. Multiple brain-enhancing lesions were found on brain MRI, with the largest mass at the right frontal lobe (Figure 1A). The patient completed 10 doses of biweekly HD-MTX (8 g/m^2) induction therapy [23] from January to June 2016, resulting in resolved disease on PET scan and complete remission (CR) on brain MRI (Figure 1B). Because of the patient's age, she did not undergo additional chemotherapy or stem cell transplant as consolidation/maintenance therapy and instead underwent surveillance with brain MRIs.

The first relapse of lymphoma was found at the right cerebellum on surveillance brain MRI in May 2017, 11 months after the completion of induction therapy with HD-MTX and 17 months after diagnosis (Figure 2A). There was no relapse of lymphoma at the original site. The patient was started on a second-line chemotherapy regimen, temozolomide and rituximab [24]. The enhanced lesion completely resolved after one cycle (4 weeks) of temozolomide and rituximab therapy (Figure 2B). However, 3 months after her first relapse, 20 months from diagnosis, a second relapse, now multifocal, was identified on brain MRI (Figure 3) in August 2017, and the patient was rechallenged with biweekly HD-MTX (8 g/m^2) treatment. After four doses of biweekly rechallenging HD-MTX therapy, 2 months after her second relapse and 22 months after diagnosis, the brain MRI showed a third-time disease progression (Figure 4). The patient was then enrolled in a clinical trial (NCT02483858), 'Study of Oral PQR309 Patients with Advanced Tumors', in November 2017 [25]. Unfortunately, she experienced a rapid decline in mental function, speech, strength, and gait. Her CNS lymphoma was significantly larger on brain MRI (fourth progression) (Figure 5). Because of this, the patient went off the trial 1 month after enrollment to the trial, and approximately 23 months from diagnosis.

After being off the trial, the patient received urgent WBRT (50 Gy, 25 fractions) and completed radiation therapy in January 2018, 2 years after the PCNSL diagnosis. As a result of WBRT, the lymphoma burden showed a significant reduction on post-radiation brain MRI (Figure 6). The patient also had improvements in strength and speech but experienced memory and hearing impairments likely due to radiation-related neurotoxicity. Given the fact that her CNS lymphoma had failed multiple treatment regimens, maintenance therapy with ibrutinib after salvage WBRT was discussed with the patient and her family members, who wished to move forward to prevent additional recurrence. The patient began 560 mg of oral ibrutinib daily as maintenance therapy in March 2018 (2 months after completion of WBRT and 26 months from diagnosis). She tolerated ibrutinib well. After 3 months of 560 mg daily ibrutinib treatment,

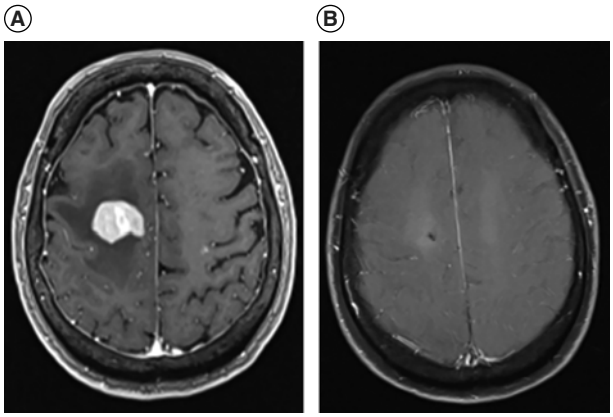

Figure 1. Brain MRIs prior to and after high dose-methotrexate treatment. **(A)** Brain MRI prior to biopsy showed homogenous enhancing masses on post contrast T1 image. **(B)** Brain MRI showed resolution of lymphoma lesions on post-contrast T1 image after induction high dose-methotrexate treatment.

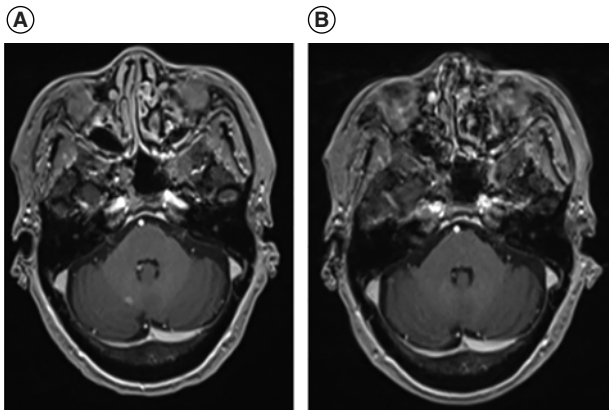

Figure 2. Brain MRIs of first relapse of primary central nervous system lymphoma and its resolution after temozolomide+rituximab treatment. **(A)** Brain MRI showed first relapse at 11 months after completion of high dose-methotrexate (HD-MTX) induction therapy, 17 months after diagnosis of primary central nervous system lymphoma. The recurrent lymphoma was seen at right cerebellum on the post-contrast T1 image. **(B)** Brain MRI showed resolution of 1st relapsed lymphoma on the post-contrast T1 image at right cerebellum after 1 cycle (4 weeks) of temozolomide (TMZ) and rituximab (RTX) therapy.

her CNS lymphoma nearly resolved (uCR). However, a follow-up brain MRI after 6 months of 560 mg daily ibrutinib treatment showed mild progression of enhancement, so her dosage of ibrutinib was increased from 560 mg to 840 mg daily. After 3 months of higher dose (840 mg) daily ibrutinib therapy, the lymphoma again nearly resolved (uCR). After 6 months of a higher dose (840 mg) of daily ibrutinib, the patient's brain MRI showed resolution of lymphoma (CR; 12 months from initiation of ibrutinib and 38 months from diagnosis). However, a lab study showed elevation of liver function tests (LFTs) on 840 mg daily dose, showing Common Terminology Criteria for Adverse Events version 5 (CTCAE v.5) grade 2 alanine aminotransferase and aspartate aminotransferase increase and CTCAE grade 3 alkaline phosphatase, and gamma-glutamyl transferase increase. The patient was asymptomatic.

Because of elevated LFTs, the dosage of ibrutinib was tapered down to 560 mg daily. Her LFTs went back to normal range after this dose reduction. In late August 2019, after nearly 18 months of ibrutinib maintenance therapy, the patient was taken off ibrutinib in accordance with the patient's and her family's wishes. Her surveillance brain MRI at 4 months after being off ibrutinib, 4 years from diagnosis, remained stable without signs of lymphoma recurrence. The disease and treatment course are illustrated in Figure 7. Consent was provided by the patient and her family to conduct a chart review, collect data for research and education purposes, and present or publish de-identified data. The patient was lost to follow-up during the coronavirus disease 2019 pandemic until 2022 when her family member updated the stable neurological condition of the patient. There had been no more brain MRI surveillance and clinic follow-ups in accordance with patient and family wishes. The patient died of a

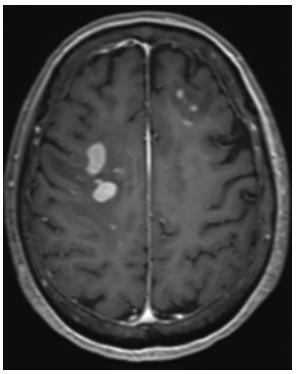

Figure 3. Brain MRI of relapsed primary central nervous system lymphoma. Brain MRI showed multifocal recurrence of lymphoma on post-contrast T1 image after 2 cycles (8 weeks) of Temozolomide (TMZ)+Rituximab (RTX) therapy, at 20 months since diagnosis.

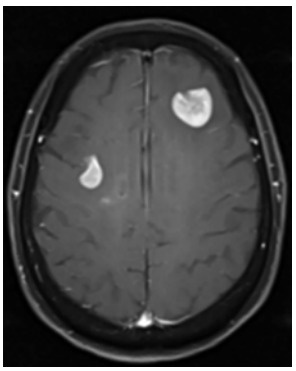

Figure 4. Brain MRI of further progressed primary central nervous system lymphoma. Brain MRI showed further progression on post-contrast T1 image after 2 cycles of (8 weeks) rechallenging biweekly high dose-methotrexate (HD-MTX), at 22 months since diagnosis.

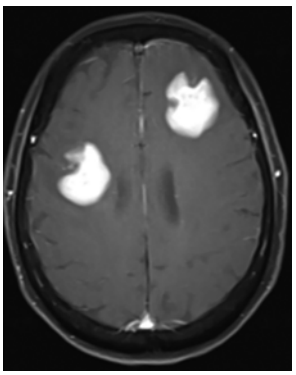

Figure 5. Brain MRI with more relapsed progressed primary central nervous system lymphoma. Brain MRI showed rapid 4th progression on post-contrast T1 image after a clinical trial therapy, at 23 months since diagnosis.

cause the family did not disclose. She survived 57 months (4.75 years) from the completion of salvage WBRT and 81 months (6.75 years) from the initial diagnosis of PCNSL.

3. Discussion

This case presentation highlights a patient with r/r PCNSL who failed multiple lines of treatment, was treated safely with single-agent ibrutinib as maintenance therapy following salvage WBRT, and survived 81 months from diagnosis. It is warranted to explore this case since radiation usually results in short remission, but this patient survived 57 months after salvage WBRT, although it is difficult to state the efficacy of the treatment based on a single case.

r/r PCNSL is not uncommon, and there are no standard therapies. Nonstandard treatment regimens include rechallenging with single-agent HD-MTX or HD-MTX-

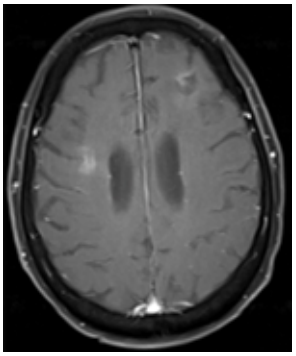

Figure 6. Brain MRI after whole brain radiation therapy. Brain MRI showed a reduction of enhanced lymphoma lesions on post-contrast T1 image after completion of WBRT, at 24 months since diagnosis.
WBRT: Whole brain radiation therapy.

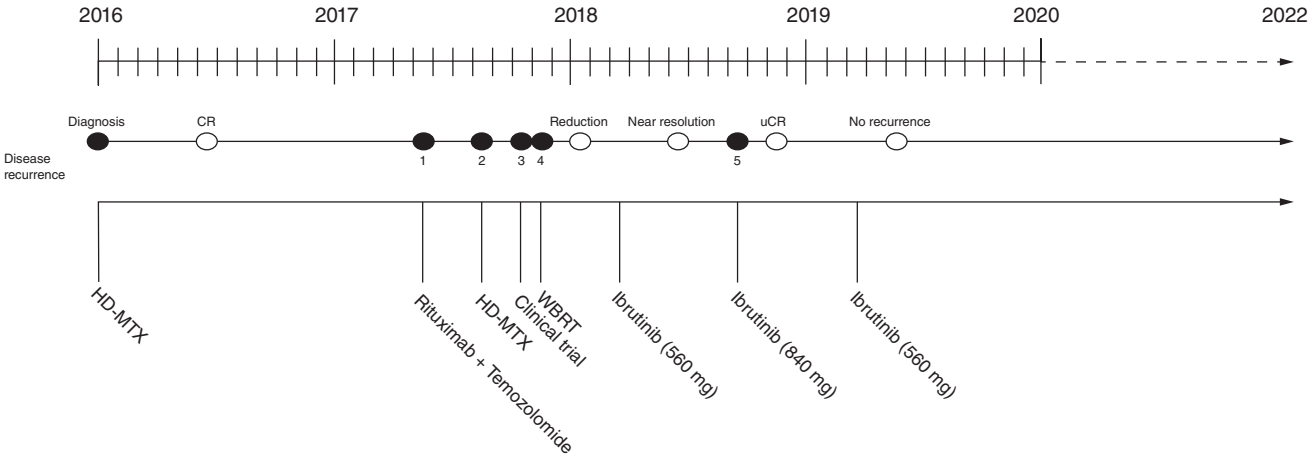

Figure 7. The disease course and treatment response. Diagnosis: Diagnosed in 2016. Disease recurrence: 1-5 disease. Black dot: with disease burden at diagnosis or recurrence (relapse/recurrence/progression). White dot: with no or mild disease burden due to partial or complete response to the treatment.
CR: Complete response; HD-MTX: High dose-methotrexate; uCR: Unconfirmed complete response; WBRT: Whole brain radiation therapy.

based regimens, rituximab plus temozolomide, other conventional chemotherapy, HDC/ASCT, or WBRT [12–14]. WBRT is usually used as a last-line salvage therapy due to its neurotoxicity [14].

In the current literature, the administration of salvage WBRT alone for r/r PCNSL results in a median OS of 10 to 16 months [15–18]; in this case, the patient survived for 57 months (4.75 years) after salvage WBRT, 81 months (6.75 years) from initial diagnosis. The prolonged survival in this case after salvage WBRT may be related to the 18 months of ibrutinib maintenance therapy. We considered the positive effect of ibrutinib against lymphoma recurrence since the patient had mild tumor progression on a lower dose (560 mg) of daily ibrutinib but experienced complete resolution of her lymphoma after 6 months of higher-dose (840 mg) daily ibrutinib. Interestingly, after reducing back to 560 mg daily dose from 860 mg daily dose due to adverse effects, no further progression of lymphoma was noted on the lower dose or even after discontinuation. The possible explanation is that 12 months of therapy with ibrutinib might be a reasonable duration for maintenance therapy to prevent the recurrence of lymphoma after salvage WBRT or induction therapy, as we reported in another case study [26].

The usual adult dose of ibrutinib is 420 mg to treat chronic lymphocytic leukemia [27] or other conditions such as Waldenström's macroglobulinemia [28]. While the typical dose to treat PCNSL is 560 mg daily in most studies [17,18], a few clinical studies have explored both a higher dose of 840 mg daily and the typical dose of 560 mg daily to treat patients with r/r PCNSL and secondary CNSL and compared the drug concentration in cerebrospinal fluid [29–31]. Mean ibrutinib concentrations in the 2 h postdosing CSF were almost doubled in the patients receiving 840 mg daily dose compared with the 560 mg daily dose [29–31]; for example, 3.992 ng/ml (range: 0.305–9.22) in patients receiving 840 mg daily dose versus 1.553 ng/ml (range: 0.991–

2.62) in patients receiving 560 mg daily dose [29]. Ibrutinib at both dose levels was tolerated with manageable adverse effects. No dose-limiting toxicity occurred during the dose-escalation portion of the study. There was no difference in CTCAE grade 3 and grade 4 adverse effect profiles between the two dose levels. The response rates between 840 mg and 560 mg treatment patients were similar but were not directly compared in the article, likely due to the small number of patients in the studies [29,30]. The authors proposed to use an 840 mg dose of ibrutinib because cerebrospinal fluid drug concentrations achieved with 840 mg were consistently above the 50% inhibitory concentration needed to induce cell death *in vitro* [29–31]. The current case was started on a typical 560 mg daily dose to treat PCNSL. Although a 560 mg daily dose has known CNS penetration [29–31], the lymphoma recurred, and the 560 mg daily dose needed to be increased to 840 mg daily to make the CR. This finding supports Grommes *et al.*'s proposal to use an 840 mg dose of ibrutinib to treat CNSL [29]. It suggests the need to push ibrutinib higher to 840 mg in individual patients with PCNSL who tolerate lower dose therapy well.

The patient tolerated ibrutinib well despite asymptomatic CTCAE grade 2 to 3 elevation of LFTs on 840 mg daily dose, which resolved after reducing the dose to 560 mg daily.

The proposal to use ibrutinib as maintenance therapy following salvage WBRT in the treatment of r/r PCNSL to extend the duration of response to the anti-lymphoma treatment is supported by prior literature studies in which single-agent ibrutinib demonstrated safety and efficacy in the treatment of newly diagnosed PCNSL as maintenance therapy [10] and in the treatment of some r/r PCNSL cases [21,22]. In one phase II study involving 29 r/r PCNSL and 15 secondary CNS lymphoma cases, treatment using single-agent ibrutinib resulted in an overall response rate of 78%, a median progression-free survival (PFS) of 4 months, and a median OS of 19.5 months [22]. In another phase II study involving 52 patients with r/r PCNSL and primary vitreoretinal lymphoma, treatment with ibrutinib yielded a median PFS of 4.8 months and a median OS of 19.2 months [21].

Conclusion

In conclusion, this case showed prolonged survival after receiving maintenance therapy with ibrutinib following salvage WBRT. From a single case, it is difficult to draw conclusions about the efficacy of this treatment. Further studies with sufficient cases should be done to examine its effectiveness and optimal duration of maintenance therapy after salvage WBRT to treat r/r PCNSL.

Summary points

- Primary CNS lymphoma (PCNSL) is an aggressive disease that originates in lymphocytes and develops in the CNS.
- Refractory or relapsed PCNSL (r/r PCNSL) is not uncommon.
- Whole-brain radiation therapy (WBRT) is usually used as a last-line salvage therapy for r/r PCNSL and yields a median survival of 10 to 16 months for patients with r/r PCNSL when used alone without maintenance therapy afterward.
- Because of past success in other studies of the treatment of r/r PCNSL, ibrutinib was used as maintenance therapy following salvage WBRT for a patient who failed multiple treatment regimens that included initial high-dose methotrexate (HD-MTX), rituximab and temozolomide, rechallenging with HD-MTX, and a clinical trial.
- The patient tolerated a daily dose of 560 mg ibrutinib well and experienced near-resolution of the disease.
- After 6 months of 560 mg daily ibrutinib treatment, mild progression of disease was detected on brain MRI, so the daily ibrutinib dosage was increased to a higher dose of 840 mg daily.
- After 6 months of a higher daily dose (840 mg) of ibrutinib treatment, complete disease resolution was detected on brain MRI.
- The patient survived for 57 months from completion of salvage WBRT with the addition of ibrutinib maintenance therapy for 18 months following WBRT.
- This case showed prolonged survival after salvage WBRT and ibrutinib maintenance therapy for relapsed PCNSL, suggesting it may be worth exploring the possible effect of ibrutinib as maintenance therapy for r/r PCNSL after salvage WBRT.

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Author contributions

S Du: study conceptualization, data collection, analysis, original manuscript writing, multiple revisions, and final approval. DB Fu: data collection, analysis, and final approval. DA Bota: validation, manuscript revisions, and final approval. XT Kong: study concept, data analysis, interpretation, manuscript revisions, and final approval. All authors read and agreed to the published version of the manuscript.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. Informed consent was obtained from the patient and her family members.

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