CASE REPORT

Primary pituitary lymphoma successfully treated with Bruton's tyrosine kinase inhibitor monotherapy: case report

Keijiro Yoshida, MD[1], Tomonari Suzuki, MD, PhD[1], Hiroki Sato, MD, PhD[2], Hiroki Kobayashi, MD[1], Reina Mizuno, MD[1], Mitsuaki Shirahata, MD, PhD[1], Tatsuya Ozawa, MD, PhD[1], Kazuhiko Mishima, MD, PhD[1]

1. Department of Neuro-oncology, Saitama Medical University International Medical Center, Hidaka, Japan
2. Department of Cerebrovascular Surgery, Saitama Medical University International Medical Center, Hidaka, Japan

Abstract

Introduction: Primary pituitary lymphoma (PPL) is a rare disease characterized by lymphoma confined to the sella or parasellar region without systemic involvement. The clinical symptoms of PPL may include headache, hypopituitarism, visual field disturbance and visual impairment. To date, there is no established standard treatment for this condition.

Here, we present a case of successful treatment with a Bruton's tyrosine kinase (BTK) inhibitor.

Case report: A 78-year-old man with a history of severe left renal insufficiency caused by retroperitoneal fibrosis, and sequential right nephrostomy, underwent brain magnetic resonance imaging (MRI) due to the altered hormonal status. An enlarged pituitary stalk was noted and led to a diagnosis of lymphocytic hypopituitarism.

Six months later, visual field disturbance and visual acuity deterioration developed, and an MRI revealed a neoplastic lesion and further enlargement of the stalk and the pituitary itself, with an obvious optic nerve compression. Expedited transsphenoidal partial resection was performed to relieve the compression. Pathophysiology led to the diagnosis of the large B-cell lymphoma of the germinal center origin. Because of the patient's poor renal function, high-dose methotrexate therapy was not an option; rather, the patient was treated with a BTK inhibitor - tirabrutinib. Symptoms improved within a week, and a follow-up MRI confirmed a marked reduction of the pituitary lesion.

Conclusion: BTK inhibitors may be considered as a first-line treatment option for PPL, especially in patients with contraindications for other treatment protocols.

Keywords: hypopituitarism; malignant lymphoma; primary pituitary lymphoma; Bruton's tyrosine kinase inhibitor; tirabrutinib

DOI: https://doi.org/10.55005/v3i1.7

Introduction

Malignant lymphomas originating from the central nervous system, or primary central nervous system lymphoma (PCNSL) account for about 3% of intracranial malignancies[1], with those arising within the sella turcica region being extremely rare[2]. Primary malignant lymphoma of the pituitary gland (primary pituitary lymphoma, PPL) is generally considered when a lymphoma is confined to the sella or parasellar region, without systemic invasion[3]. The relevant clinical symptoms of include headache, hypopituitarism, and visual field and acuity disturbances.

Primary pituitary lymphoma is extremely rare, lacks evidence regarding treatment, and is typically treated the same way as PCNSL[4]. High-dose methotrexate (MTX) and the whole-brain radiation therapy of 30–40 Gy, is the standard of treatment for newly diagnosed PCNSL in Japan. In patients with relapsed disease, high-dose MTX with rituximab-based retreatment; monotherapy with rituximab, topotecan, and temsirolimus; as well as the Bruton's tyrosine kinase (BTK) inhibitors; have been tried, but the optimal therapy is yet to be elucidated[5].

Bruton's tyrosine kinase (BTK), a downstream mediator of the B-cell antigen receptor (BCR), has been linked to a number of B-cell malignancies. BTK inhibitors suppress tumor cell growth by inhibiting BTK activity, and have been shown to be effective against PCNSL[5]. Tirabrutinib is a second-generation BTK inhibitor that is more potent and selective than those of the first generation[6]. It is approved in Japan for the treatment of relapsed/refractory PCNSL, and it's urine excretion accounts for only about 10% of the total[5].

With a PPL only partially resected, and limited chemotherapeutic options due to the renal insufficiency, we aimed to complement the initial surgery with tirabrutinib monotherapy.

Case report

A 45-year-old male patient was admitted to the infectious diseases hospital on December 18, 2021. He was treated for a SARS-CoV-2 infection complicated by bilateral poly-segmental pneumonia. Since admission, the patient had a severe headache (up to 8 points on a visual analog scale).

A 78-year-old male was referred to our department by an ophthalmologist because of visual field disturbance and visual acuity deterioration; with a suspected pituitary neoplasm. Except for the bitemporal hemianopsia, the patients other neurological status was unremarkable.

Six months prior, the patient was diagnosed with lymphocytic hypopituitarism after brain magnetic resonance imaging (MRI) revealed an enlarged pituitary stalk. Anterior and posterior pituitary hormones secretions were insufficient, and hormone replacement therapy involving levothyroxine, hydrocortisone, and desmopressin was started. Symptoms improved, and he was followed up with outpatient visits.

Repeated MRI revealed a pituitary lesion, enlarging the pituitary gland and the stalk, extending from the sella turcica to the cephalic region and compressing the optic nerve (***Figure 1***).

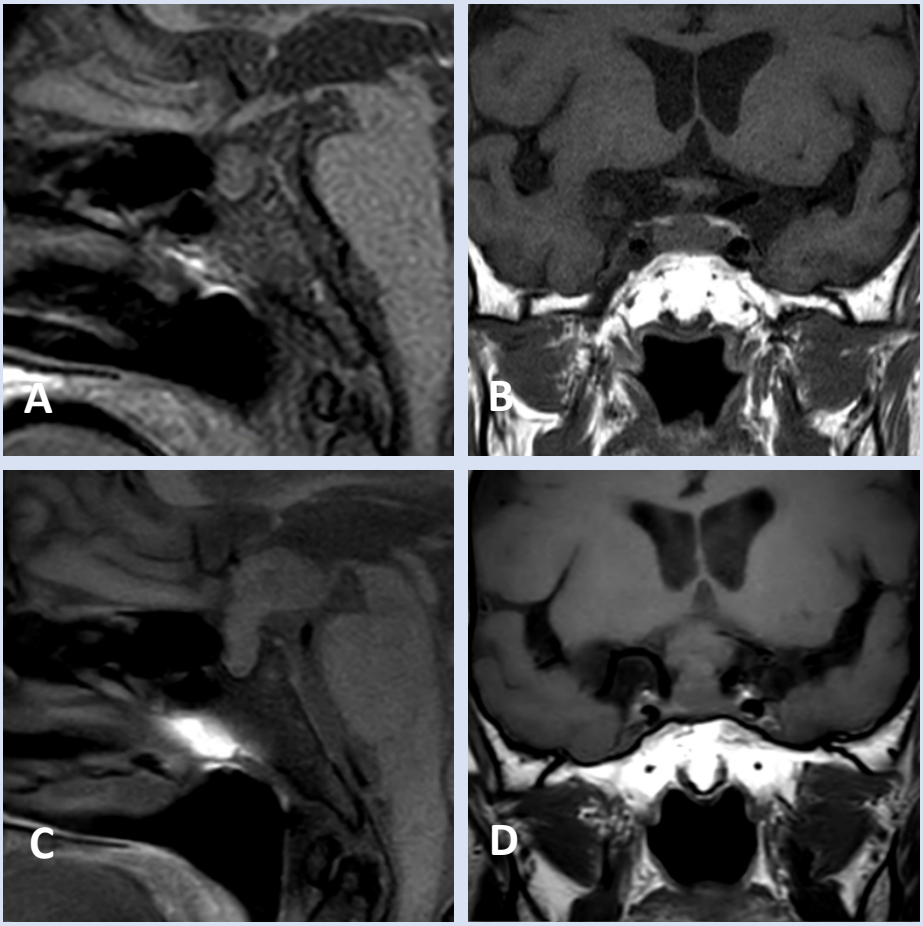

Figure 1. MRI simple T1-weighted image (sagittal and coronal planes): A. at the first visit to the previous hospital; B. the tumor had enlarged 6 months after the first visit.

The patient had a medical history of retroperitoneal fibrosis, left renal insufficiency, and right nephrostomy, which required regular replacement. Blood laboratory tests revealed low levels of total protein, albumin, and an estimated glomerular filtration rate (32.6 mL/min/L), and elevated levels of C-reactive protein, IgG, IgA, IgM, IgG4, prolactin, and anti-neutrophil cytoplasmic antibody. The patient also exhibited low levels of anterior pituitary hormones and slightly elevated levels of ProGRP (90.1 g/mL) and soluble IL-2 receptor (661 U/mL); however, the tumor markers were negative. IgG4-related hypopituitarism was considered, therefore, a whole-body FDG positron emission tomography (PET) scan and CSF examination were performed, but no abnormalities were detected.

Since the visual field disturbances and visual impairment progressed, an expedited transsphenoidal resection was performed.

Histopathological examination revealed a lesion of lymphocyte-like atypical cell proliferation with a necrotic background. Immunohistochemistry indicated that the atypical cells were positive for CD20 and BCL6 staining and negative for MUM1 staining, and had an MIB1 labeling index of ~70%; thus, a diagnosis of large B-cell lymphoma of germinal center origin was established (***Figure 2***). Bone marrow aspiration, to investigate the possibility of bone marrow involvement, obtained no malignant cells.

Although high-dose MTX is the recommended first-line treatment according to the national protocol for PCNSL[7], because of his renal impairment and age, the patient received oral tirabrutinib. Within a week of starting oral administration of this drug, the lesion exhibited shrinkage, and the patient's visual field disturbance and visual acuity improved. However, after 6 weeks of oral administration, severe pneumonia caused by cytomegalovirus emerged, leading to the discontinuation of tirabrutinib. Eight weeks after discontinuing the treatment, a follow-up MRI showed that the tumor disappearance was maintained (***Figure 3***).

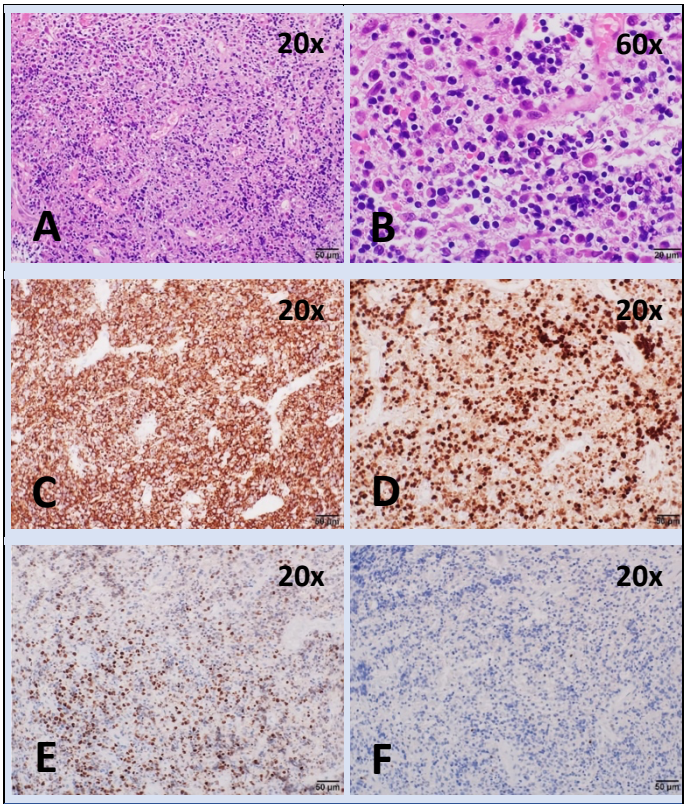

Figure 1. Pathology of the pituitary tumor biopsy. A. 20x hematoxylin-eosin staining showed a lesion consisting of lymphocyte-like atypical cell proliferation on a background of necrosis and immunostaining B. 60x: C. CD20 staining positive, D. MIB1 labeling rate about 70%, E. BCL6 staining positive, and F. MUM1 staining negative led to a diagnosis of large B-cell lymphoma, germinal center B-cell-like type.

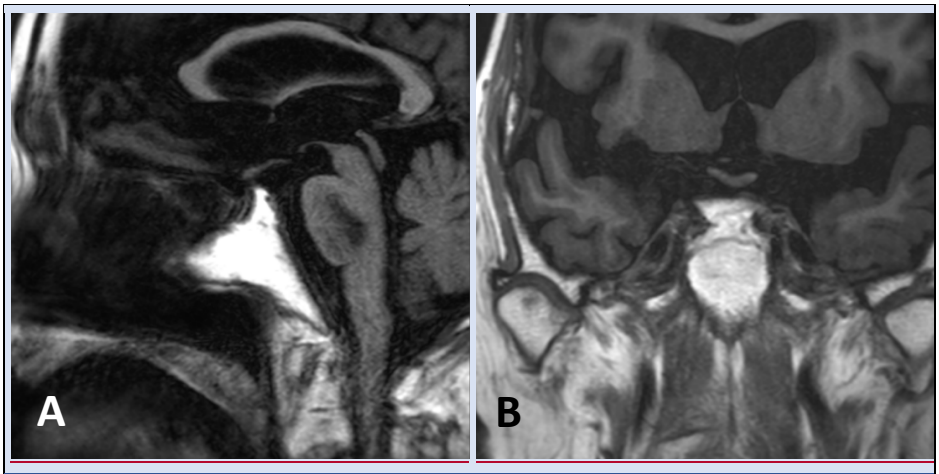

Figure 1. MRI T1-weighted image (sagittal and coronal planes) 8 weeks after chemotherapy.

Discussion

To the best of our knowledge, this is the first case report of PPL treated with tirabrutinib. Even more, the treatment was successful, and the BTK inhibitor was used as an adjuvant monotherapy after partial surgical resection.

Primary central nervous system lymphoma involving only the pituitary gland is rare, with only about 40 adult cases reported to time. Due to its specifies, one previous study suggested that PPL should be considered a separate entity from PCNSL, as the pituitary gland (as well as the pineal) lack a blood–brain barrier and pose a different embryological structure from the brain parenchyma, thus constituting for distinguish[4,8].

Diffuse large B-cell lymphoma is the most common type of PCNSL[9] and this applies to the PPL as well. With the emerge of the gene expression profiling, two subgroups were identified: the germinal center B cell-like (GCB); and the activated B cell-like and heterogenous subtypes (Non-GCB)[10]. Unlike our case, the activated B cell-like is the most common subtype of PCNSL, usually ascribed as the reason for the poor prognosis[11]. BTK inhibitors inhibit the proliferation and induce apoptosis of GCB PNCSL cell lines, and appear efficient in this particular subtype[12], thus leading to the good response in our patient as well.

Primary central nervous system lymphoma is generally treated with chemotherapy based on high-dose MTX, which bypasses the blood–brain barrier, but since the pituitary gland does not have a blood–brain barrier it allows for the wider variety of efficient options including: high-dose MTX[13]; cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (CHOP) therapy[14]; but also, other protocols with varying efficacy[3,15,16]. Because of impaired renal function and the patients advanced age, neither high-dose MTX-based nor CHOP therapy[7] were considered an option in our case, and oral tirabrutinib was chosen instead.

Surgery is usually not considered in PCNSL[17], however, due to the frequent compression-related symptoms in PPL, partial resection to debulk the lesion and obtain histopathology was fully justified, especially due to the worsening despite symptomatic treatment. Radiotherapy was frequently used in PPL[18,19], but, due to the increased toxicity[20], recently reported therapies, omitted the radiotherapy from their armamentarium[3,4,21], and so did us.

The tumor exhibited marked shrinkage 1 week after the tirabrutinib administration was started. Regardless of the premature treatment discontinuation after 6 weeks because of severe infection and omitted radiotherapy, complete remission was maintained for the next 2 months, suggesting that the treatment was ultimately safe and effective.

Conclusion

After initial surgical resection and histopathological confirmation, tirabrutinib appears as a viable alternative treatment option for patients with PPL, even more so in patients who are unable to receive other agents for any given reason. Future prospective studies are needed to establish the efficacy of BTK inhibitor chemotherapy on the outcome and prognosis of patients with PPL.

Disclosures

Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Funding: No funding was received for this research.

Correspondence

Keijiro Yoshida

✉ Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, 1397-1, Yamane, Hidaka-shi, Saitama 350-1298, Japan

☎ +818030397650

@ ky38841@5931.saitama-med.ac.jp

References

1. Giustina A, Gola M, Doga M, Rosei EA. Clinical review 136: Primary lymphoma of the pituitary: an emerging clinical entity. J Clin Endocrinol Metab. 2001;86(10):4567-4575. doi:10.1210/jcem.86.10.7909
2. Freda PU, Post KD. Differential diagnosis of sellar masses. Endocrinol Metab Clin North Am. 1999;28(1):81-vi. doi:10.1016/s0889-8529(05)70058-x
3. Duan L, Liu J, Zhang Y, et al. Primary Pituitary Lymphoma in Immunocompetent Patients: A Report on Two Case Studies and the Review of Literature. Front Endocrinol (Lausanne). 2021;11:562850. Published 2021 Feb 4. doi:10.3389/fendo.2020.562850
4. Tarabay A, Cossu G, Berhouma M, Levivier M, Daniel RT, Messerer M. Primary pituitary lymphoma: an update of the literature. J Neurooncol. 2016;130(3):383-395. doi:10.1007/s11060-016-2249-z
5. Narita Y, Nagane M, Mishima K, et al. Phase I/II study of tirabrutinib, a second-generation Bruton's tyrosine kinase inhibitor, in relapsed/refractory primary central nervous system lymphoma. Neuro Oncol. 2021;23(1):122-133. doi:10.1093/neuonc/noaa145
6. Okita Y, Kano-Fujiwara R, Nakatsuka SI, Honma K, Kinoshita M. Histological verification of the treatment effect of tirabrutinib for relapsed/refractory primary central nervous system lymphoma. Exp Hematol Oncol. 2021;10(1):29. doi:10.1186/s40164-021-00222-5
7. Nakamura H, Takami H, Yanagisawa T, et al. The Japan Society for Neuro-Oncology guideline on the diagnosis and treatment of central nervous system germ cell tumors. Neuro Oncol. 2022;24(4):503-515. doi:10.1093/neuonc/noab242
8. Konishi J, Miki Y, Asato R. Imaging Diagnosis of Hypothalamic Pituitary Diseases. Nihon Naika Gakkai Zasshi. 1994;83(12):2117-21. doi: 10.2169/naika.83.2117.
9. Deckert M, Engert A, Brück W, et al. Modern concepts in the biology, diagnosis, differential diagnosis and treatment of primary central nervous system lymphoma. Leukemia. 2011;25(12):1797-1807. doi:10.1038/leu.2011.169
10. Mahadevan A, Rao CR, Shanmugham M, Shankar SK. Primary central nervous system diffuse large B-cell lymphoma in the immunocompetent: Immunophenotypic subtypes and Epstein-Barr virus association. J Neurosci Rural Pract. 2015;6(1):8-14. doi:10.4103/0976-3147.143171
11. Yang XL, Liu YB. Advances in Pathobiology of Primary Central Nervous System Lymphoma. Chin Med J (Engl). 2017;130(16):1973-1979. doi:10.4103/0366-6999.211879
12. Zheng X, Ding N, Song Y, Feng L, Zhu J. Different sensitivity of germinal center B cell-like diffuse large B cell lymphoma cells towards ibrutinib treatment. Cancer Cell Int. 2014;14(1):32. Published 2014 Apr 3. doi:10.1186/1475-2867-14-32
13. Quintero Wolfe S, Hood B, Barker J, Benveniste RJ. Primary central nervous system lymphoma mimicking pituitary apoplexy: case report. Pituitary. 2009;12(1):76-79. doi:10.1007/s11102-008-0084-8
14. Rudnik A, Larysz D, Blamek S, et al. Primary pituitary lymphoma. Folia Neuropathol. 2007;45(3):144-148.
15. Ogawa A, Sugano H, Inoue T, Fujihara M, Matsumoto S, Tsuchiyama Y, et al. Malignant Lymphoma Presented with Thickned Pituitary Stalk and Hypopituitalism. Nihon Naika Gakkai Zasshi. 2008;97(6):1324-6. doi: 10.2169/naika.97.1324.
16. Huang YY, Lin SF, Dunn P, Wai YY, Hsueh C, Tsai JS. Primary pituitary lymphoma presenting as hypophysitis. Endocr J. 2005;52(5):543-549. doi:10.1507/endocrj.52.543
17. Schaff LR, Grommes C. Primary central nervous system lymphoma. Blood. 2022;140(9):971-979. doi:10.1182/blood.2020008377
18. Ravindra VM, Raheja A, Corn H, et al. Primary pituitary diffuse large B-cell lymphoma with somatotroph hyperplasia and acromegaly: case report. J Neurosurg. 2017;126(5):1725-1730. doi:10.3171/2016.5.JNS16828
19. Romeike BF, Joellenbeck B, Stein H, et al. Precursor T-lymphoblastic lymphoma within a recurrent pituitary adenoma. Acta Neurochir (Wien). 2008;150(8):833-836. doi:10.1007/s00701-008-1585-y
20. Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol. 2010;11(11):1036-1047. doi:10.1016/S1470-2045(10)70229-1
21. Ban VS, Chaudhary BR, Allinson K, Santarius T, Kirollos RW. Concomitant Primary CNS Lymphoma and FSH-Pituitary Adenoma Arising Within the Sella. Entirely Coincidental? Neurosurgery. 2017;80(1):E170-E175. doi: 10.1093/neuros/nyw003