—Case Reports—

Primary Central Nervous System Lymphoma in a Patient with Down Syndrome

Ami Shibata[1,2], Fumio Yamaguchi[3,4], Kazuma Sasaki[2], Shoji Yokobori[2] and Akio Morita[3]

[1]Department of Emergency and Critical Care Medicine, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan
[2]Department of Emergency and Critical Care Medicine, Nippon Medical School, Tokyo, Japan
[3]Department of Neurosurgical Surgery, Nippon Medical School, Tokyo, Japan
[4]Department of Neurosurgery for Community Health, Nippon Medical School, Tokyo, Japan

Intracranial tumors are rare in persons with Down syndrome. Although germ cell tumors and gliomas have been reported in Down syndrome, primary central nervous system lymphoma (PCNSL) has not. We report a case of PCNSL in a 48-year-old man with Down syndrome and no history of malignant tumors. He visited our hospital for evaluation of left hemiparesis and gait disturbance. A thorough examination revealed brain tumors, and analysis of a biopsy specimen of the tumor confirmed a diagnosis of PCNSL. The final pathological diagnosis was diffuse large B-cell lymphoma of the central nervous system. Chemotherapy with rituximab, methotrexate, procarbazine, and vincristine was administered, and whole-brain irradiation was planned in conjunction with chemotherapy. It is unclear whether chromosomal abnormalities related to Down syndrome were involved in the development of PCNSL. Further molecular biological analysis may clarify the mechanism of combined Down syndrome and PCNSL.
(J Nippon Med Sch 2023; 90: 346–350)

Key words: brain tumor, Down syndrome, lymphoma, PCNSL, primary central nervous system lymphoma

Introduction

Down syndrome is one of the most common chromosomal abnormalities, and the average lifespan of affected persons is reportedly 28 years shorter than that of the general population[1]. Despite a decline in birth rates, the prevalence of Down syndrome has risen recently because of the increasing percentage of women older than 30 years who give birth[2]. Down syndrome is associated with numerous phenotypes, including congenital heart defects, leukemia, Alzheimer disease, and Hirschsprung disease[3]. Although leukemia is a common malignant tumor in persons with Down syndrome[3–5], intracranial tumors are rare[6]. Embryonal tumors are the most common intracranial tumors associated with Down syndrome[6], whereas other solid tumors, such as gliomas, central nervous system primitive neuroectodermal tumors, and medulloblastomas, have rarely been reported[7,8]. We report a case of primary central nervous system lymphoma (PCNSL) in a man with Down syndrome. His family provided informed consent for publication of this report.

Case Report

A 48-year-old man with Down syndrome was referred by another hospital for evaluation of a brain tumor. His chief complaint was gait disturbance, and he had been unable to walk on his own for approximately 2 months before he visited our hospital. No complications associated with Down syndrome were evident before he visited our hospital.

His Glasgow Coma Scale score was E4V2M5, which was identical to his score before the present symptoms. Because of his cognitive limitations, he was unable to fol-

Correspondence to Ami Shibata, MD, PhD, Department of Emergency and Critical Care Medicine, Nippon Medical School Tama Nagayama Hospital, 1–7–1 Nagayama, Tama, Tokyo 206–8512, Japan
E-mail: 068m1044@nms.ac.jp
https://doi.org/10.1272/jnms.JNMS.2023_90-502
Journal Website (https://www.nms.ac.jp/sh/jnms/)

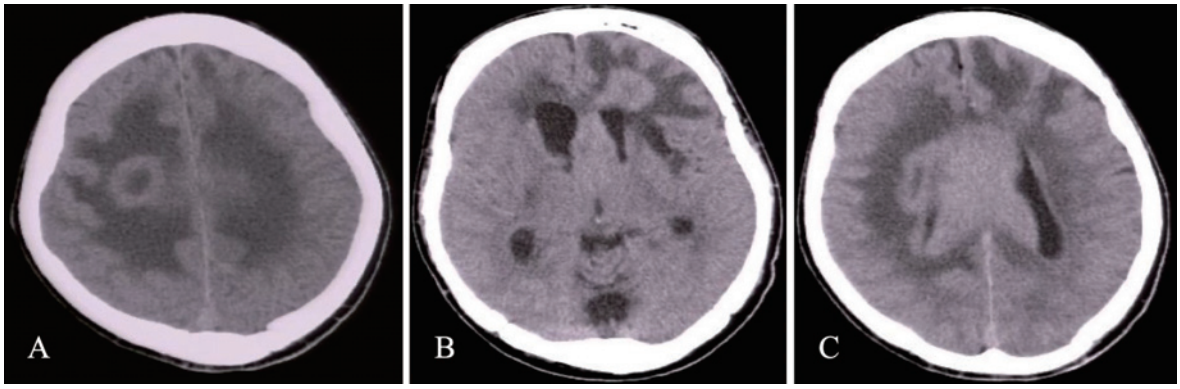

Fig. 1 Preoperative brain computed tomography scans at approximately 1 month after symptom onset. The tumors were accompanied by marked edema (A, B), were located in both hemispheres, and were centered on the corpus callosum (C).

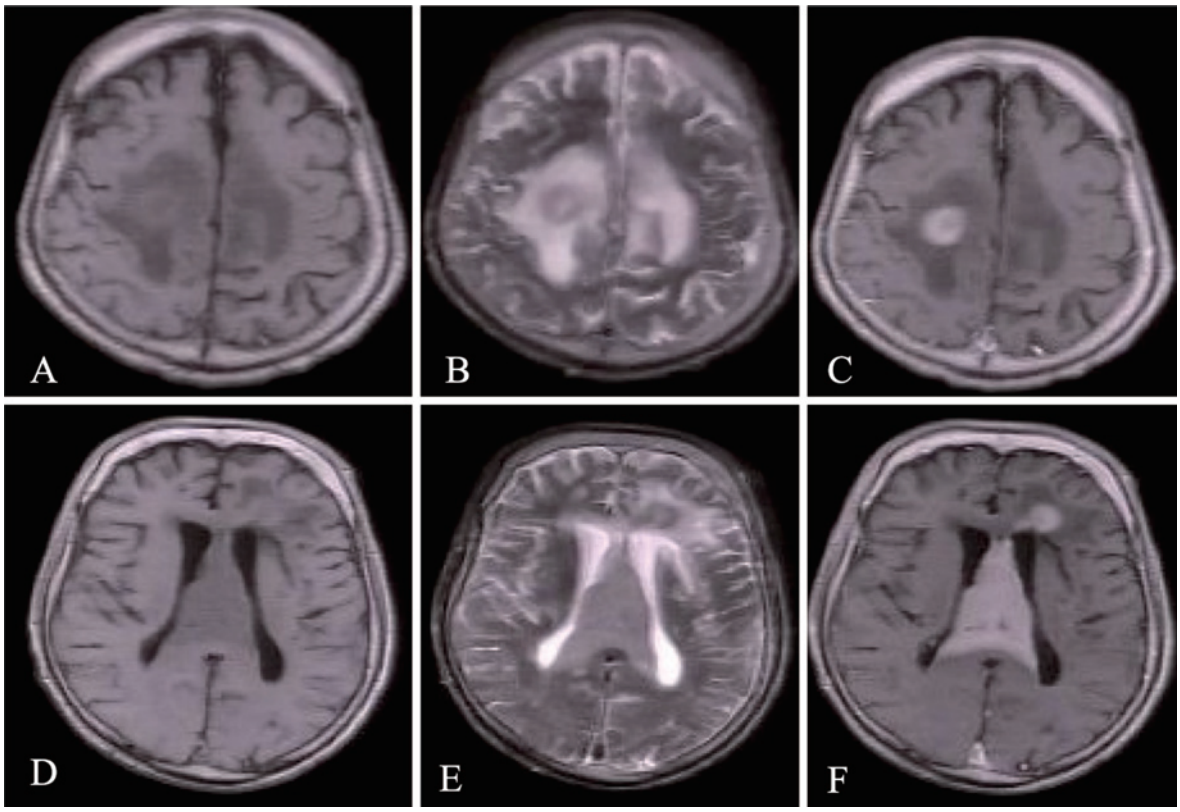

Fig. 2 Preoperative brain magnetic resonance imaging scans: T1-weighted images (A and D), T2-weighted images (B and E), and gadolinium-enhanced T1-weighted images (C and F). The tumors were isointense on T1-weighted images and moderately hyperintense on T2-weighted images. The contrast medium was distributed uniformly and markedly. Brain edema was noticeable near the tumors, and the corpus callosum was extensively enhanced.

low our instructions. He had mild hemiparesis in the left upper and lower limbs and had difficultly walking on his own. His facial appearance was characteristic of Down syndrome.

Cranial computed tomography (CT) scanning at the referring hospital revealed that the tumors, which were accompanied by marked edema, were located in both hemispheres and had spread symmetrically across the corpus callosum (**Fig. 1**). Brain magnetic resonance imaging (MRI) showed tumor isointensity on T1-weighted images, moderate hyperintensity on T2-weighted images, and hyperintensity on diffusion-weighted images. The tumors were distributed along the ventricular wall and were uniformly enhanced by gadolinium (**Fig. 2**). Chest

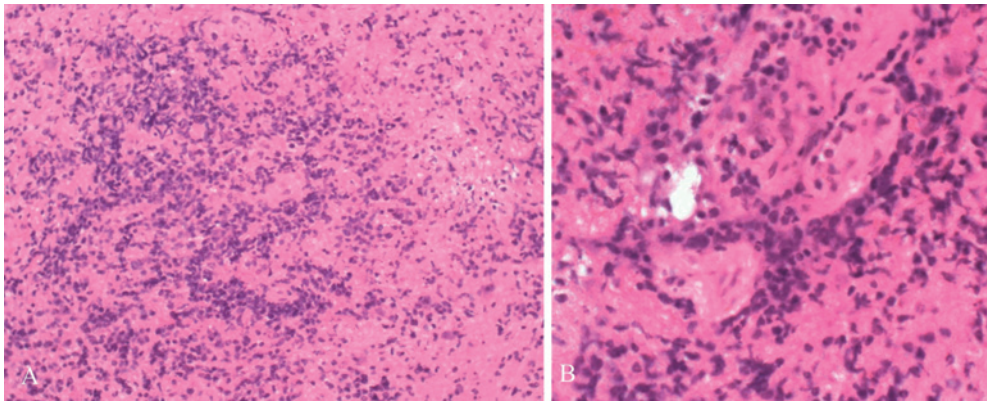

Fig. 3 Pathological appearance. (A) Low-power image of hematoxylin and eosin (HE) staining (10× magnification). Large, atypical lymphocyte-like tumor cells with oval and round nuclei and sparse cytoplasm were growing. (B) High-power image of HE staining (20× magnification). Tumor cells infiltrated and proliferated in the perivascular lumen and exhibited perivascular cuffing.

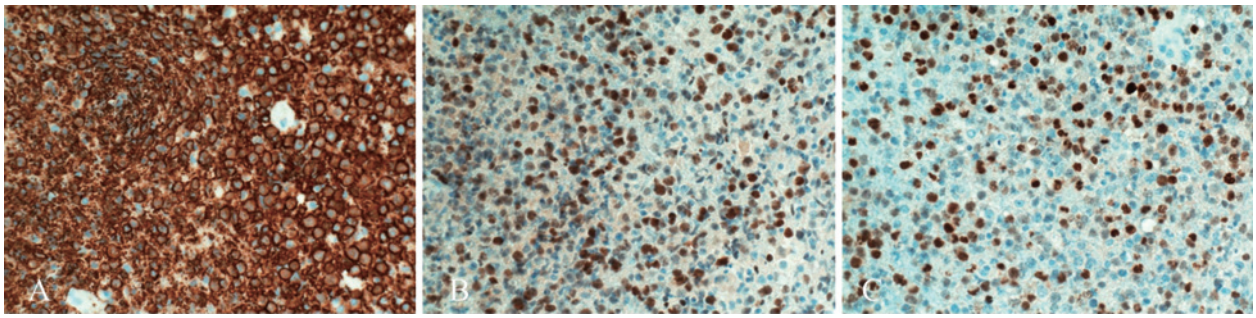

Fig. 4 Immunohistochemistry. Tumor cells were strongly positive for CD 20 (A) and positive for BCL6 (B) and MUM1 (C).

and abdominal CT scans showed no evidence of malignancy, and levels were within normal ranges for the serum tumor markers soluble interleukin-2 receptor, carcinoembryonic antigen, carbohydrate antigen 19-9, neuron specific enolase, and prostate specific antigen. There was no evidence of tumor metastasis.

A tumor biopsy was performed with the assistance of a navigation system that targeted a mass in the left frontal lobe. Intraoperative pathological findings showed proliferation of atypical lymphocyte-like cells, without necrosis or nuclear palisading suggestive of glioblastoma, which is consistent with lymphoma. Hematoxylin and eosin staining revealed diffuse proliferation of large, atypical lymphocyte-like tumor cells and perivascular cuffing, in which tumor cells clustered in the perivascular space (**Fig. 3**). Immunohistochemistry indicated that the cells were positive for CD20, BCL6, and MUM1 (**Fig. 4**). The final pathological diagnosis from the permanent specimen was diffuse large B-cell lymphoma (DLBCL) of the central nervous system.

In addition to steroids, chemotherapy with rituximab, methotrexate, procarbazine, and vincristine was initiated on postoperative day 3. Brain CT scanning performed 12 days postoperatively showed tumor shrinkage and marked improvement in cerebral edema. Whole-brain radiotherapy was planned after five to seven courses of this treatment and was to be followed by cytarabine treatment.

Discussion

PCNSL is rare, accounting for 1-2% of all cases of non-Hodgkin lymphoma[9,10]. The annual incidence of PCNSL is estimated to be 0.48 per 100,000 persons per year (1.41 per 100,000 persons aged ≥65 years). PCNSL is an aggressive non-Hodgkin lymphoma, and its histological features usually include large B cells[11]. PCNSL accounts for about 5% of primary tumors, and incidence has increased in recent years, especially among elderly adults[12,13]. PCNSL is reported to be more common in elderly and immunocompromised adults[14] but is not known to be associated with chromosomal abnormalities, such as those related to Down syndrome.

Down syndrome is one of the most common chromosomal abnormalities; the incidence rate is 1 in 792 infants[15]. It is a congenital disorder caused by an abnormality in chromosome 21. The average life expectancy of people with Down syndrome has increased substantially, from 25 years in 1983 to 60 years in 2020[16]. Although leukemia is associated with Down syndrome[3,5], intracranial tumors are rare and not well characterized in this population[6,17]. The mechanism by which Down syndrome patients develop leukemia has been described previously. Genetic analysis reported that mutations in GATA-1 are specific for leukemia in Down syndrome. A possible mechanism is that GATA-1 mutations occur in hematopoietic stem cells of trisomy 21. Other genetic mutations then occur, which results in leukemia. However, the mechanism by which brain tumors develop in Down syndrome is unclear.

In 2011, an autopsy study of 1514 persons with Down syndrome revealed that only 4 (0.26%) had intracranial tumors[18]. In 2001, a study of the association of Down syndrome with intracranial and spinal cord tumors[6] found that 36 cases of intracranial tumor were associated with Down syndrome, but none of these tumors was PCNSL. Of these 36 cases, germ cell tumors and gliomas were most common. In particular, 61% of patients younger than 15 years were reported to have germ cell tumors. To our knowledge, no case of PCNSL associated with Down syndrome has been previously reported.

The development of genomic medicine has been a remarkable recent achievement in the treatment of brain tumors[19,20]. In DLBCL, homeostatic activation of B-cell receptor signaling is believed to be the main mechanism of disease onset and resultant tumor growth. Bruton tyrosine kinase inhibitors inhibit the B-cell receptor signaling pathway and are reportedly effective[21].

Micro-RNAs (miRNA) are short noncoding sequences involved in the biological regulatory process and are biomarkers that help identify early cancer through pathogenesis[22]. MicroRNA-155 (miR-155) is overexpressed in persons with Down syndrome and contributes directly and indirectly to the onset and progression of Down syndrome[23]. MiR-155 is assumed to be related to B-cell responses, and overexpression of miR-155 suppresses inositol phosphatase (SHIP1) expression[24]. In DLBCL, elevated miR-155 levels and consequent diminished SHIP1 expression were triggered by stimulation of inflammatory cytokine tumor necrosis factor alpha[25]. These results suggest that miR-155 overexpression may contribute to DLBCL onset in persons with Down syndrome, but this remains a matter of speculation. The absence of previous reports of PCNSL in Down syndrome suggest that the combination might be an incidental finding. However, it is possible that DLBCL is caused by new changes in miR-155 in persons with Down syndrome. Molecular biological studies might help clarify a mechanism underlying the combination of Down syndrome and PCNSL.

Acknowledgement: The authors thank Enago for reviewing the language of the manuscript.

Conflict of Interest: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. O'Leary L, Hughes-McCormack L, Dunn K, Cooper SA. Early death and causes of death of people with Down syndrome: a systematic review. J Appl Res Intellect Disabil. 2018;31(5):687–708.
2. O'Nualláin S, Flanagan O, Raffat I, Avalos G, Dineen B. The prevalence of Down syndrome in County Galway. Ir Med J. 2007;100(1):329–31.
3. Asim A, Kumar A, Muthuswamy S, Jain S, Agarwal S. "Down syndrome: an insight of the disease". J Biomed Sci. 2015;22(1):41.
4. Lee P, Bhansali R, Izraeli S, Hijiya N, Crispino JD. The biology, pathogenesis and clinical aspects of acute lymphoblastic leukemia in children with Down syndrome. Leukemia. 2016;30(9):1816–23.
5. Mateos MK, Barbaric D, Byatt SA, Sutton R, Marshall GM. Down syndrome and leukemia: insights into leukemogenesis and translational targets. Transl Pediatr. 2015;4(2):76–92.
6. Satgé D, Monteil P, Sasco AJ, et al. Aspects of intracranial and spinal tumors in patients with Down syndrome and report of a rapidly progressing Grade 2 astrocytoma. Cancer. 2001;91(8):1458–66.
7. Satgé D, Stiller CA, Rutkowski S, et al. A very rare cancer in Down syndrome: medulloblastoma. Epidemiological data from 13 countries. J Neurooncol. 2013;112(1):107–14.
8. Alexandrov PN, Percy ME, Lukiw WJ. Chromosome 21-Encoded microRNAs (mRNAs): impact on Down's syndrome and trisomy-21 linked disease. Cell Mol Neurobiol. 2018;38(3):769–74.
9. Nakamaki T. [Recent advances in the treatment of primary central nervous system lymphoma]. Brain Nerve. 2014;66(8):969–79. Japanese.
10. Schorb E, Finke J, Ferreri AJ, et al. High-dose chemotherapy and autologous stem cell transplant compared with conventional chemotherapy for consolidation in newly diagnosed primary CNS lymphoma--a randomized phase III trial (MATRix). BMC Cancer. 2016;16:282.
11. Olson JE, Janney CA, Rao RD, et al. The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. Cancer. 2002;95(7):1504–10.
12. Doucet S, Kumthekar P, Raizer J. Primary central nervous system lymphoma. Curr Treat Options Oncol. 2013;14(2):185–97.

13. Löw S, Han CH, Batchelor TT. Primary central nervous system lymphoma. Ther Adv Neurol Disord. 2018;11: 1756286418793562.
14. Lukas RV, Stupp R, Gondi V, Raizer JJ. Primary central nervous system lymphoma-PART 1: epidemiology, diagnosis, staging, and prognosis. Oncology (Williston Park). 2018;32(1):17–22.
15. Kaczorowska N, Kaczorowski K, Laskowska J, Mikulewicz M. Down syndrome as a cause of abnormalities in the craniofacial region: a systematic literature review. Adv Clin Exp Med. 2019;28(11):1587–92.
16. Tsou AY, Bulova P, Capone G, et al. Medical care of adults with Down syndrome: a clinical guideline. JAMA. 2020;324(15):1543–56.
17. Satgé D, Sommelet D, Geneix A, Nishi M, Malet P, Vekemans M. A tumor profile in Down syndrome. Am J Med Genet. 1998;78(3):207–16.
18. Ehara H, Ohno K, Ito H. Benign and malignant tumors in Down syndrome: analysis of the 1514 autopsied cases in Japan. Pediatr Int. 2011;53(1):72–7.
19. Mukasa A. Genome medicine for brain tumors: current status and future perspectives. Neurol Med Chir (Tokyo). 2020;60(11):531–42.
20. Tamura R, Toda M. Historic overview of genetic engineering technologies for human gene therapy. Neurol Med Chir (Tokyo). 2020;60(10):483–91.
21. 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):122–33.
22. Paramasivam G. Micro-RNA (miRNA): a biomarker to identify novel compounds in drug discovery and delivery for cancer therapy. Curr Drug Discov Technol. 2021;18(6): e130921188092.
23. Mahernia S, Hassanzadeh M, Adib M, et al. The possible effect of microRNA-155 (miR-155) and BACE1 inhibitors in the memory of patients with down syndrome and Alzheimer's disease: design, synthesis, virtual screening, molecular modeling and biological evaluations. J Biomol Struct Dyn. 2022;40(13):5803–14. Epub 2021 Jan 22.
24. Keck-Wherley J, Grover D, Bhattacharyya S, et al. Abnormal microRNA expression in Ts65Dn hippocampus and whole blood: contributions to Down syndrome phenotypes. Dev Neurosci. 2011;33(5):451–67.
25. Pedersen IM, Otero D, Kao E, et al. Onco-miR-155 targets SHIP1 to promote TNFalpha-dependent growth of B cell lymphomas. EMBO Mol Med. 2009;1(5):288–95.

(Received, March 1, 2022)
(Accepted, April 21, 2022)
(J-STAGE Advance Publication, May 30, 2022)