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Primary Burkitt lymphoma of the CNS in an immunocompetent elderly woman

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Primary central nervous system Burkitt lymphoma is rare and often occurs in patients in an immune deficient state, especially in acquired immunodeficiency syndrome. Herein, we present a report on an immunocompetent 77-year-old woman, who was healthy in the past but complained of general malaise and dizziness for three days before admission. A computed tomographic scan revealed a butterfly-shaped mass in the pericallosal white matter, extending to the left basal ganglion and peduncle. The mass was homogenously enhanced after contrast injection. Magnetic resonance images exhibited a huge, enhancing and infiltrative tumor involving the genu to splenium of the corpus callosum, bilateral radiata, bilateral corticospinal tract, hippocampi, posterior limb of the internal capsule and left cerebral peduncle and ventrolateral pons, causing prominent vasogenic edema of the bilateral parietal, left frontal and temporal lobes. She underwent stereotactic biopsy of the brain lesion, and the pathology confirmed the diagnosis of Burkitt lymphoma. Postoperative intrathecal chemotherapy and palliative radiotherapy were administered, and the patient died six months later because of systemic sepsis.

Key words: cerebral Burkitt lymphoma, intrathecal chemotherapy

INTRODUCTION

Primary extranodal lymphoma can arise in various sites including the gastrointestinal tract, bone, thyroid, skin, orbit, testis, lung and breast, among others. However, primary malignant lymphoma of the central nervous system (CNS) is uncommon[1]. By definition, primary CNS lymphoma is an extranodal lymphoma with no extracranial manifestations and the absence of systemic disease[2]. The incidence is low and constitutes 0.3%-1.5% of all primary brain tumors[3-5] and 0.7%-0.8% of all lymphomas[1].

Over recent decades, the incidence of primary CNS lymphoma has increased, and it often occurs in patients with immune deficient states, especially in acquired immunodeficiency syndrome (AIDS)[6-10]. Patients with cardiac and renal transplantation, IgA deficiency, or even Wiskott-Aldrich syndrome are also in the high-prevalence groups[11-12]. Primary CNS lymphomas appear at a single or multicentric location in the cerebral hemispheres, especially periventricular areas[2]. Primary CNS lymphomas can be of nearly all types of non-Hodgkin lymphoma, and high-grade B cell lymphoma with large cell morphology is predominant[13]. Burkitt lymphoma, a malignant B cell lymphoma has been only rarely reported in the CNS. To our knowledge, there are few cases that have been reported in the English-language literature and only one case report in the East Asian area[14].

Here, we present a rare case of cerebral Burkitt lymphoma, diagnosed by stereotactic brain biopsy and treated with a combination of intrathecal chemotherapy and radiotherapy.

CASE REPORT

An immunocompetent 77-year-old female with a history of hypertension complained of progressive bilateral limb weakness, dizziness, and conscious-state disturbances over the three days preceding admission. After admission, her vital signs were: blood pressure 136/78 mmHg, heart rate 90/min, and respiratory rate 18/min. The patient was stuporous; however, neurological examinations revealed no remarkable findings except for a Glasgow Coma Scale

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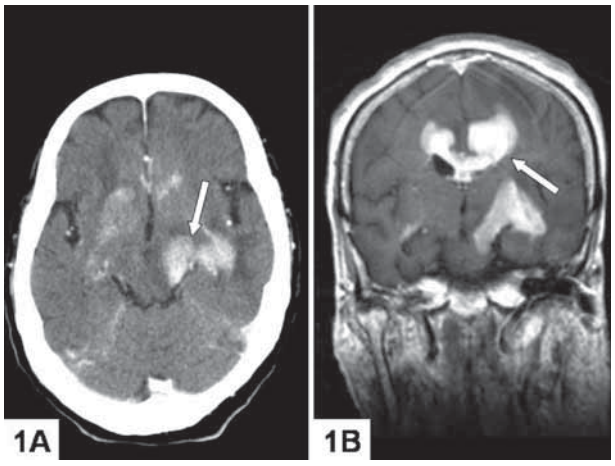

Fig. 1 Cranial contrast-enhanced CT (1A) and T1-weighted MRI (1B) demonstrated an irregular tumor mass (arrows) in cross and longitudinal sections respectively which displaying butterfly-shaped pattern with involving the pericallosal region, posterior periventricular white matter, orbitofrontal lobes, right basal ganglion, left temporal lobe, thalamus, cerebral peduncle of midbrain and the left lateral pons with profound perifocal edema.

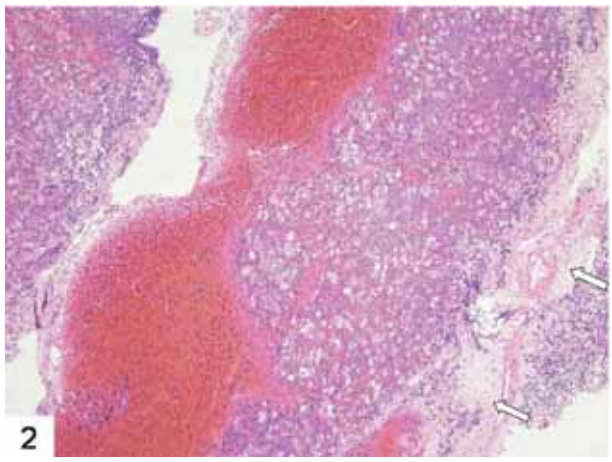

Fig. 2 Histopathology of Burkitt lymphoma. The sections of the biopsy specimen showed pictures of diffusely monotonous infiltration of the lymphoma cells, focally imparted by benign macrophages and displaying a "starry sky" growth pattern in lower power field (H&E, 200X). Hemorrhage and adjacent brain tissue invasion by lymphoma cells were also seen (arrows).

score of 8 (E2M4V2).

Serum laboratory investigations showed negative results for HIV and hepatitis B and C infections but were positive for Epstein-Barr virus. Cranial computed tomography (CT) revealed an irregular butterfly-shaped mass located in the pericallosal region. Contrast-enhanced CT showed homogenous enhancement of a mass occupying the bilateral pericallosal regions, involving the left basal ganglion and cerebral peduncle (Fig. 1A). Cranial magnetic resonance imaging (MRI) also demonstrated a huge, enhancing infiltrative tumor involving the genu to splenium of the corpus callosum, bilateral radiata, bilateral corticospinal tracts, hippocampi, posterior limb of the internal capsule and left cerebral peduncle and ventrolateral pons, causing prominent vasogenic edema of the bilateral parietal, left frontal and temporal lobes (Fig. 1B). A malignant glioma or lymphoma was strongly suspected, and a diagnostic stereotactic biopsy was performed. Three biopsy strips were obtained, measuring up to 1.6 cm in length. Pathological examinations revealed Burkitt lymphoma characterized by a diffuse monotonous infiltration of lymphoma cells with interspersed macrophages, focally displaying "starry sky" features (Fig. 2). The lymphoma cells were medium sized, containing round to mild irregular nuclei, clumped chromatin and multiple basophilic nucleoli (Fig. 3A). The lymphoma cells were also immunohistochemically positive for the pan-B maker CD20 (Fig. 3B) and Epstein — Barr virus latent membrane protein 1 (EBV-LMP1) (Fig. 3C), and the Ki-67 proliferating index determined by Ki-67 immunostaining was increased to nearly 100%. The cells were negative for CD3. Based on the clinical presentation, serum results, imaging studies, pathological morphology and immunohistochemical analysis, a primary cerebral Burkitt lymphoma was diagnosed. One week after the biopsy, an Ommaya catheter was inserted into the lateral ventricle for the purpose of intrathecal chemotherapy with methotrexate 8 mg/m^2 weekly. Radiotherapy with 180 cGy 20 times daily (total 36 Gy) was subsequently administered. The neurological deficits improved, and the patient's level of consciousness returned to normal after these treatments. However, she died six months later from severe complications of aspiration pneumonia leading to severe septic shock.

DISCUSSION

Primary extranodal lymphoma can arise in different sites, including the gastrointestinal tract, bone, thyroid, skin, orbit, testis, lung, and breast, among others. Primary malignant lymphoma of the central nervous system (CNS) is uncommon[1]. By definition, primary CNS lymphoma is an extranodal lymphoma arising with no extracranial mani-

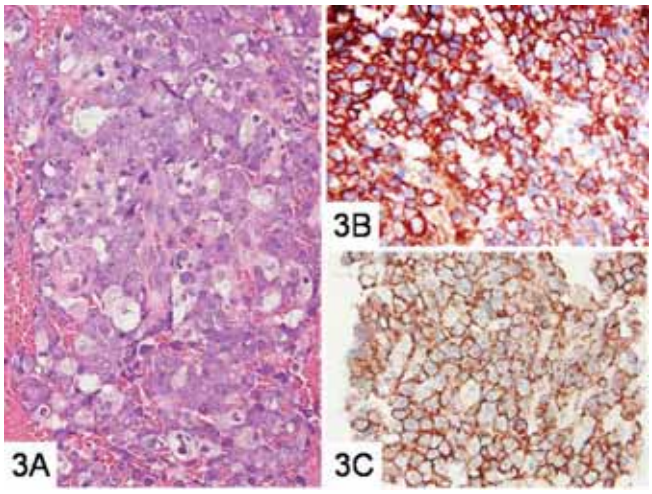

Fig. 3 Histopathology and immunohistochemically analysis of Burkitt lymphoma. The lymphoma cells were medium-sized, containing round to mild irregular nuclei, clumped chromatin and multiple basophilic nucleoli, and intermixed with digested macrophages (3A, H&E, 400X). The lymphoma cells immunohitochemically expressed the characteristic pan-B marker CD20 (3B, 400X) and EBV-LMP1 (3C, 400X).

festations and the absence of systemic disease[2]. Their incidence is rare, and the tumors constitute 0.3%-1.5% of all primary brain tumors[3-5] and 0.7%-0.8% of all lymphomas[1]. Burkitt lymphoma, a malignant B cell lymphoma, has been rarely reported in the CNS[14].

A study of 25 series yielded a total of 241 cases of primary intracranial malignant lymphoma, with a peak age incidence between 55 and 65 years, and a male:female ratio of 1.4-2.0:1[15]. The main symptoms of the patients arise from increased intracranial pressure (IICP). IICP may be caused by a blockage in the ventricles of the brain that leads to a build-up of cerebrospinal fluid and/or by swelling around the tumor itself[15]. The results of IICP are headaches, sickness, vomiting and changes in eyesight. Seizures are also common with this type of tumor, and the patient may appear to be confused at times, with changes in behavior and/or personality[15]. In the presented case, the patient suffered from the severe symptoms and signs by presenting of stuporous ccconsciousness, IICP and a decreased Glasgow Coma Scale of 8 (E2M4V2). These changes were due to a bulky high-grade brain tumor mass with a short doubling time[15,16].

To our knowledge, few cases have been reported in the English-language literature[14]. Spath-Schwalbe et al. reported a case of a highly malignant B-cell lymphoma of the Burkitt type that responded partially to methotrexate, with full remission achieved for more than one year[16]. Toren et al. described a six-year-old immunocompetent girl with Guillain-Barre syndrome and primary CNS Burkitt lymphoma. After receiving aggressive systemic and intrathecal chemotherapy, complete remission was achieved for more than two years[17]. Hochberg et al. reported an immunocompetent patient with primary CNS lymphoma and serological evidence of recent primary infection with the Epstein-Barr virus, suggesting a case of Burkitt lymphoma[18]. Monabati et al. also reported a case of an immunocompetent patient, in whom testing for the Epstein-Barr virus produced negative results, who had a primary CNS lymphoma in which histopathological studies revealed a high-grade non-Hodgkin lymphoma of the small, noncleaved, Burkitt type[19]. In summary, cases of primary CNS Burkitt lymphoma with or without concomitant infection with the Epstein-Barr virus, although very rare, have been reported and may represent another unusual variant of primary CNS lymphoma.

Primary CNS Burkitt lymphoma must be proved by histopathological features, EBV infection, and a constant genetic translocation[20]. The characteristic morphologic features of Burkitt lymphoma are a “starry sky” feature seen in lower-power fields and diffuse infiltration by monotonous lymphoma cells with multiple nucleoli. The nuclear size of the lymphoma cells is similar to that of macrophages. Multiple small areas of macrophages digesting apoptotic lymphoma cells produce the “starry sky” pattern[20]. The Burkitt lymphoma cells can express membrane IgM with light chain restriction and B-cell-association antigens (CD19, CD20 and CD22), CD10, BCL2 and BCL6[20-22]. The cells are negative for CD5, CD23, CD34 and TdT[20-22]. In addition, a high proliferating activity of nearly 100%, as revealed by Ki-67 staining, is another specific characteristic of the tumor[20,21]. EBV infection also plays an important role in CNS Burkitt lymphoma[21,22], and almost all cases have a translocation of the *MYC* gene at chromosome 8q24 to the Ig heavy chain region on chromosome 14 at band q32 or, less commonly, to the light chain locus at 2q11[20-22]. The presented case was diagnosed by the tumor cells being immunohistochemically positive for CD20 and EBV-LMP1, with nearly 100% of cells positive for Ki-67, as well as anti-EBV antigen being identified in the serum.

MRI is the best diagnostic method for evaluating a patient with cerebral neoplasia. The typical image of a CNS lymphoma appears as an isointense signal on T1-weighted images, a hyperintense signal on T2-weighted images, and diffuse enhancement after gadolinium injection[5]. The tumor characteristically exhibits surround-

ing edema with indistinct borders. Unlike brain metastases or malignant gliomas, ring enhancement is rarely seen[5]. Magnetic resonance spectroscopy may provide additional diagnostic information. Primary CNS lymphomas have a marked elevation of lipid and a much higher choline: creatine ratio than all grades of astrocytoma[5]. In addition, CT is the diagnostic approach of choice in patients suspected of having an intracranial malignant lymphoma and may strongly suggest the specific diagnosis. The CT scan serves as an effective instrument for the stereotactic biopsy and the specimen could provide definitively histopathological diagnosis. We therefore performed a CT-guided stereotactic biopsy in this patient. The method offers a suitable therapeutic choice without delay and without more invasive surgical intervention. The usefulness of stereotactic biopsy is therefore emphasized.

The treatment of primary CNS lymphoma includes chemotherapy and radiotherapy[5]. While radiotherapy alone results in a median survival of only 12 to 18 months[21], a median survival of more than 40 months has been achieved with combined radiotherapy and chemotherapy[22]. High-dose chemotherapy protocols that include methotrexate are similarly effective in terms of tumor response and extension of survival[23-26]. The chemotherapies used were a combination of preradiation cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP). A few patients are reported to have had their survival prolonged by CHOP plus whole brain radiotherapy, although many of these patients also received intrathecal methotrexate. The risk of long-term neurotoxicity in patients treated with combined intravenous and intraventricular chemotherapy that includes methotrexate and cytarabine is low. Accordingly, this treatment regimen seems to be more favorable than combined radiotherapy and chemotherapy protocols, which have a known high risk of severe neurotoxicity, particularly in older patients[27]. High-dose methotrexate is known to be the most important agent for the treatment of primary CNS lymphoma[25]. The dosage can range from 1 mg/m^2 to 8 mg/m^2. However, dosages of more than 3 mg/m^2 are thought to be more reliable in these patients[25]. Based on the study of the Radiation Therapy Oncology Group (RTOG), treatment strategies for radiotherapy should be designed to give 45 Gy in total dose[21]. Significant risks of severe, irreversible neurotoxicity, characterized by dementia, ataxia, and incontinence, have also been reported after combined therapy[21].

Our patient appeared to have a good therapeutic response without significant complications after weekly intrathecal chemotherapy with high-dosage methotrexate (8 mg/m^2) via an Ommaya reservoir. The palliative radiation treatment with a dosage of 180 cGy daily (total 45 Gy) was also applied. Despite poor cardiopulmonary function, the consciousness of the patient improved to baseline status after one week of treatment, and she appeared to be quite well in the following months. However, she died six months later from severe complications of aspiration pneumonia leading to septic shock. Therefore, intense post-treatment care should be emphasized to prevent complications in these patients.

In conclusion, we presented herein a report of an immunocompetent 77-year-old female with primary CNS Burkitt lymphoma. Stereotactic technique for brain biopsy provided a definitive diagnosis. Intrathecal chemotherapy combined with hyperfractionated radiotherapy as adjuvant treatment could also be applied in the patient with cardiopulmonary dysfunction. Despite the poor prognosis of this kind of lymphoma, early diagnosis and advanced treatment remain the keystones for the patients with primary CNS Burkitt lymphoma.

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