Gliomatosis Cerebri Mimicking Chemotherapy-Induced Leukoencephalopathy in a Patient with non-Hodgkin’s Lymphoma

Joji Inamasu¹, Masashi Nakatsukasa¹, Takumi Kuramae¹, Yoshihiro Masuda², Kazuhiro Tomiyasu² and Taketo Yamada³

Abstract

Patients with hematological malignancies may develop white matter lesions, which are usually associated with chemotherapy. Magnetic resonance imaging (MRI) is the imaging modality of choice for identifying chemotherapy-induced, or “toxic”, leukoencephalopathy. Brain biopsy in patients with hematological malignancies suspected of sustaining toxic leukoencephalopathy has rarely been performed, because its characteristic MRI findings are considered pathognomonic. Biopsy may be indicated in atypical cases, however, and it may yield unexpected results. We describe a case with white matter lesions that developed in an elderly man treated for non-Hodgkin’s lymphoma. The lesions, initially diagnosed with toxic leukoencephalopathy based on MRI findings, turned out to be gliomatosis cerebri.

Key words: biopsy, chemotherapy, gliomatosis cerebri, non-Hodgkin’s lymphoma, toxic leukoencephalopathy


Introduction

The efficacy and safety of intensive chemotherapy for patients with hematological malignancies, i.e., malignant lymphoma and leukemia, has been established. However, there are some adverse effects associated with its use. Leukoencephalopathy is a rare but well-known complication of the intensive chemotherapy in such patients. Recently, reports on chemotherapy-induced, or “toxic” leukoencephalopathy have increased (1-8). Magnetic resonance imaging (MRI) of the brain is the imaging modality of choice for the differential diagnosis of white matter lesions that develop in patients with hematological malignancies (2, 3, 5, 6, 8). Biopsy of the white matter lesions, which is performed less frequently nowadays, is still important because the white matter lesions may be associated with an unexpected etiology. We present a case of gliomatosis cerebri (GC) manifesting as progressive multifocal white matter lesions that developed in an elderly man who had been treated for cervical non-Hodgkin’s lymphoma (NHL).

Case Report

A 71-year-old man presented to our clinic with a progressive homonymous hemianopsia of the left side. He had been treated for NHL (diffuse large B-cell) which had originated from the parotid gland for 17 years. He had undergone multiple regimens of intensive chemotherapy for NHL including MACOP-B (methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), only in the former of which methotrexate was included. The last time methotrexate was used was more than 15 years previously, and it was administered neither intrathecally nor in high dose intravenously. The most recent chemotherapy cycle he received was 24 months earlier, and the regimen included rituximab and etoposide. He had also undergone irradiation to the cervical lymph nodes, 30 Gy in total dose, 17 years previously. He was alert and oriented,
and other than hemianopsia, he showed no neurologic deficits. His Karnofsky Performance Status (KPS) was 90. A brain MRI was obtained which demonstrated white matter lesions in the bilateral occipital lobes and in the right frontal lobe. The lesions were iso- to hypointense on T1-weighted image (Fig. 1A), and there was no enhancement with gadolinium. The lesions were depicted as hyperintense spots on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (Fig. 1B, C). Serum biochemistry including soluble interleukin-2 receptor (IL-2R) was unremarkable. Because of the previous use of intensive chemotherapy for NHL, toxic leukoencephalopathy was suspected. He was followed at the outpatient clinic, since treatment of toxic leukoencephalopathy is supportive. One month later, however, he came back with worsening symptoms: his visual field defects became bilateral and deteriorated to the point of cortical blindness. Although there were no signs of dementia or personality change, he was mildly depressed probably due to the acute progression of his symptoms. His KPS deteriorated to 70. Neither focal nor generalized abnormality was noted on electroencephalogram, and cerebrospinal fluid (CSF) study obtained by a lumbar puncture yielded normal findings. A repeat MRI showed progression of the white matter lesions (Fig. 2A-E). The lesions were depicted as mixed intensity on diffusion-weighted imaging (DWI) and high intensity on apparent diffusion coefficient (ADC) map (Fig. 2E). Since the rapid worsening of his condition was considered unusual for toxic leukoencephalopathy which is generally self-limited, and since non-invasive methods alone seemed to be insufficient for establishing the histological diagnosis, he was admitted and a brain biopsy was performed to identify the cause, with preoperative differential diagnoses including lymphomatosis cerebri (9, 10). The surgical specimen was obtained from the right frontal lobe under image-guidance, with the assumption that the white matter lesions in the three lobes were homogenous. A pathology work-up demonstrated an area of abnormally dense cellularity consisting of large, atypical cells that resembled astrocytes (Fig. 3). Immunostaining for glial fibrillary acidic protein was positive, implying that the tumorous cells were of astrocytic origin. There were very few areas of focal necrosis or neovascularization, however. Immunostaining for CD45RB, a surface marker for lymphocytes, was negative. These findings led to the histological diagnosis of Grade III astrocytoma (11). He was clinically diagnosed with GC, because of involvement of the multiple lobes and absence of mass formation by the lesion (11). After several cycles of oral temozolomide administered at a dose of 150 mg/m² for 5 days every 4 weeks, his visual symptoms improved substantially. Twelve months after initiation of the temozolomide treatment, he remains neurologically stable, his KPS returned to 90, and marked shrinkage of the lesion was noted on MRI (Fig. 4). Permission to present his experience to medical professionals was given.

Discussion

Leukoencephalopathy is a rare but well-known complication of intensive chemotherapy for patients with hematological malignancies. Although methotrexate is the agent associated with toxic leukoencephalopathy most frequently (1, 3, 6, 8), other agents, including 5-fluorouracil and its derivative carmofur, and monoclonal antibodies have also been reported to cause the neurotoxicity (12, 13). Although patients with acute lymphoblastic leukemia seem to be most susceptible to toxic leukoencephalopathy (14, 15), those with NHL may also suffer from the complication (16). Recently, reports on toxic leukoencephalopathy have
although there are no widely accepted classifications. Although toxic leukoencephalopathy is mostly self-limiting and reversible, cases with rapid progression with fulminant course are reported (6, 7). The subtype has been termed disseminated necrotizing leukoencephalopathy (6, 7).

MRI is the imaging modality of choice for the differential diagnosis of white matter lesions that develop in patients with hematological malignancies (1, 3, 6, 8). In addition to multifocal hyperintense spots both on T2- and FLAIR sequences, hyperintensity on DWI sequence seems to be indicative of toxic leukoencephalopathy (15). On T1-weighted image, iso- or hypointense spots may or may not be enhanced with gadolinium. In the great majority of the reported cases, the diagnosis of toxic leukoencephalopathy has been made without performing a brain biopsy. In the present patient, a brain biopsy yielded an unexpected histological finding of grade III astrocytoma. Because of its multi-lobar involvement and diffuse parenchymal invasion without creating a mass, the tumor fulfilled the diagnostic criteria of GC (11).

Gliomatosis cerebri is a glial tumor of unknown etiology and histological origin (11, 17, 18). There have been few cases of secondary GC that developed as a consequence of treatment for hematological malignancies in the medical literature (19). Although secondary non-GC gliomas are known to develop in patients with hematological malignan-
cies later in their course, they are associated with prior cranial irradiation almost invariably (20, 21). With microarray gene expression profiling, several genes which might be useful in subtyping of patients with GC have been identified (22). In the present patient, it is unlikely that prior radiation therapy for cervical NHL triggered the development of GC, because the radiation field covered only the parotid gland and cervical lymph nodes and did not cover the brain. Thus, the causal relationship between intensive chemotherapy and GC remains unclear. The unusual localization of the tumor, which seemed to be noncontiguous, also needs explanation, since typical GC spreads into multiple lobes via the corpus callosum (17, 18). Tensor tractography may be useful in visualizing the spread of GC which may otherwise not be seen with conventional MRI sequences (23). Temozolomide was shown to be effective in prolonging the survival in one-third of patients with GC (24). The median progression-free survival and overall survival was 16 months and 29 months for that population respectively (24), and our patient must be monitored closely for the probable recurrence.

In retrospect, the present patient might not have been compatible with classic “toxic” leukoencephalopathy from several aspects. First, the white matter lesions developed more than a year after the last cycle of chemotherapy, despite the fact that toxic leukoencephalopathy develops within several weeks to months of the completion of chemotherapy. Second, the use of methotrexate was more than 15 years previously, and it was neither administered intrathecally nor in high dose, both of which are known risk factors for the development of toxic leukoencephalopathy (1, 3, 6, 8). Unlike CHOP chemotherapy (16), toxic leukoencephalopathy associated with MACOP-B regimen has never been reported in literature (25). Whether the MACOP-B chemotherapy is truly free of the complication remains unclear, however, since the regimen had become obsolete by early 1990s when MRI, the diagnostic modality of choice for toxic encephalopathy, became widely available to physicians (26). Third, the lesions were depicted as mixed intensity spots on DWI and high intensity on ADC map in our patient, while typical toxic leukoencephalopathy lesions are depicted as high intensity on DWI and low intensity spots on ADC map, respectively (15, 27). The lack of gadolinium enhancement despite rapid radiographic progression might have been another key to rule out toxic encephalopathy. Magnetic resonance spectroscopy and positron emission tomography are promising imaging modalities that may facilitate the noninvasive differentiation of toxic leukoencephalopathy from tumorous lesions (28, 29). Even with these sophisticated techniques, however, the radiological and histological diagnoses may contradict each other, making the case for biopsy (29).

In summary, GC that developed in a patient with cervical NHL was reported. Brain biopsy is useful in the differential diagnosis of white matter lesions in patients with hematological malignancies whose clinical or radiographic findings are not typical for toxic leukoencephalopathy.

References

3. Haykin ME, Gorman M, van Hoff J, Fulbright RK, Baehring JM. Diffusion-weighted MRI correlates of subacute methotrexate-