Can we distinguish atypical primary brain lymphoma from glioblastoma multiforme by looking at the non-enhancing tumor?

Introduction

Preoperative differentiation between primary central nervous system lymphoma (PCNSL) and glioblastoma (GBM) is important since the strategy of treatment depends on the preoperative diagnosis of brain tumors. Wide surgical resection and concomitant treatment with radiotherapy plus temozolomide are performed for GBM [1], whereas stereotactic biopsy and high-dose methotrexate treatment as well as radiation therapy are performed for PCNSL. PCNSL with atypical findings can be easily misdiagnosed as GBM, which may lead to unnecessary surgical resection.

As is well known, PCNSL commonly occurs in the periventricular white matter, basal ganglia, and corpus callosum, although the brainstem and spinal cord are less frequently involved [2]. Solitary lesions are seen in 70% of patients, and multi-focal lesions may be observed more frequently in immunocompromised patients [2]. PCNSL usually shows hyperdense on non-contrast CT and homogeneous contrast enhancement, but sometimes the enhancement is mild, has a ring pattern, or is even absent [3]. Findings including hemorrhage, necrosis, and heterogeneous enhancement inside the tumors are

less common in patients without acquired immune deficiency syndrome (AIDS). Thus, atypical PCNSL is seemingly defined as PCNSL that has features including hemorrhage, necrosis, or heterogeneous enhancement [4].

Regarding imaging parameters, lower apparent diffusion coefficient (ADC) values, lower cerebral blood volume (CBV), and higher FDG uptake suggest PCNSL rather than GBM; however, some overlaps are usually observed [4-6]. Previously, the ADC radiomics model using contrast-enhancing solid areas revealed useful results in showing better diagnostic performance [4]. This is probably because the radiomics analysis is focused on the enhancing solid area, while “atypical” features of PCNSL are usually derived from necrosis or hemorrhage, not the solid area [4].

As written in the recent paper [7], image findings may help differentiate between PCNSL and GBM. This study included 158 patients (70 GBMs, 29 atypical PCNSLs, and 59 typical PCNSLs). ROIs were placed on the solid component of the tumor, and the relative ADC values were obtained. Maximum CBF (CBFmax) was measured from the arterial spin labeling referring to the contrast-enhanced T1-weighted imaging, and the volumes of non-enhancing tumor (nET) and whole tumor (wT) were also measured. As a result, multiple-parameter models including the nET volume ratio (nET/wT), rADCmean, and CBFmax showed the highest AUC (0.960) [7], which is comparable to the previous

study (AUC of 0.984) [4]. The DeLong test for comparison of AUCs may be required, but a two-parameter model using the nET volume ratio and CBFmax also showed a high AUC (0.949) [7]. The other two-parameter models also showed high AUCs (rADCmean and CBFmax, AUC of 0.929; rADCmean and nET volume ratio, AUC of 0.924) [7].

The rates of atypical features of PCNSL (hemorrhage, necrosis, and heterogeneous enhancement) were not thoroughly discussed, but imaging findings may prevent misdiagnosis as GBM and unnecessary surgical resection of atypical PCNSL [7]. In terms of clinical management, the evaluation of intratumoral hemorrhage is important, especially in the stereotactic biopsy. Intratumoral susceptibility signal on susceptibility weighted imaging was reported to be associated with postoperative hemorrhage after stereotactic biopsy, and therefore atypical PCNSL with hemorrhage should be carefully treated during biopsy [8].

Although differentiation between GBM and PCNSL has been a classic research theme, since the 2021 WHO Classification of CNS Tumors was introduced, many changes have been made to advance molecular diagnostics [9]. Molecular parameters have now been added as biomarkers of grading and for further estimating prognosis [9]. Regarding GBM, “glioblastoma, IDH-wildtype” is the only successor; however, glioblastoma, IDH-wildtype, WHO grade 4 will be diagnosed even in cases that appear

histologically lower grade when any one of the following is observed in IDH-wildtype diffuse astrocytoma: TERT promoter mutation, EGFR amplification, or +7/−10 copy number changes [9]. The need to differentiate GBM from PCNSL will continue in the era of WHO 2021, but additional considerations for molecular GBM are also required.

In summary, when encountering atypical features of PCNSL (hemorrhage, necrosis, heterogeneous enhancement), the values of the nET volume ratio, rADCmean, and CBFmax may lead to a correct preoperative diagnosis, and a careful stereotactic biopsy will be expected.

References

1 Stupp R, Mason WP, van den Bent MJ, et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987-996

2 Jimenez de la Pena MD, Vicente LG, Alonso RC, Cabero SF, Suarez AM, de Vega VM (2017) The Multiple Faces of Nervous System Lymphoma. Atypical Magnetic Resonance Imaging Features and Contribution of the Advanced Imaging. Curr Probl Diagn Radiol 46:136-145

3 Sutherland T, Yap K, Liew E, Tartaglia C, Pang M, Trost N (2012) Primary central nervous system lymphoma in immunocompetent patients: a retrospective review of MRI features. J Med Imaging Radiat Oncol 56:295-301

4 Kang D, Park JE, Kim YH, et al (2018) Diffusion radiomics as a diagnostic model for atypical manifestation of primary central nervous system lymphoma: development and multicenter external validation. Neuro Oncol 20:1251-1261

5 Nakajima S, Okada T, Yamamoto A, et al (2015) Differentiation between primary central nervous system lymphoma and glioblastoma: a comparative study of parameters derived from dynamic susceptibility contrast-enhanced perfusion-weighted MRI. Clin Radiol 70:1393-1399

6 Nakajima S, Okada T, Yamamoto A, et al (2015) Primary central nervous system lymphoma and glioblastoma: differentiation using dynamic susceptibility-contrast perfusion-weighted imaging, diffusion-weighted imaging, and (18)F-fluorodeoxyglucose positron emission tomography. Clin Imaging 39:390-395

7 Atypical Primary Central Nervous System Lymphoma and Glioblastoma: Multiparametric Differentiation based on Non-enhancing Volume, Apparent Diffusion Coefficient, and Arterial Spin Labeling. European Radiology

8 Tanji M, Mineharu Y, Sakata A, et al (2023) High intratumoral susceptibility

signal grade on susceptibility-weighted imaging: a risk factor for hemorrhage after stereotactic biopsy. J Neurosurg 138:120-127

9 Louis DN, Perry A, Wesseling P, et al (2021) The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol 23:1231-1251