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The challenge of adequate imaging surveillance in primary central nervous system lymphoma

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See the article by Tabouret et al., pp. 422–429.

The necessity of regular surveillance in patients after completion of therapy for primary CNS lymphoma (PCNSL) is unclear, and the optimal frequency of regular imaging has not been defined.[1] For patients enrolled in clinical studies, guidelines of the International Primary CNS Collaborative Group (IPCG) have recommended regular follow-up every 3months for 2 years, then every 6 months for an additional 3 years, and annual controls for another 5 years (ie, until 10 years of follow-up have been completed).[2] According to this consensus, follow-up comprises a physical exam and MRI including a T1-weighted contrast-enhanced scan.[2] Ophthalmological investigation for vitreoretinal lymphoma and cerebrospinal fluid analysis may also be indicated depending on initial manifestation and clinical suspicion.[2]

The clinical usefulness of regular MRI at follow-up has been supported by a recent retrospective study of 256 PCNSL patients with relapsed or refractory disease.[3] This analysis identified asymptomatic versus symptomatic relapse/progression as a favorable prognostic factor and therefore suggests that early detection of relapse by MRI at regular follow-up may benefit asymptomatic patients, at least if salvage treatment is considered.[3] Early detection of tumor recurrence in patients with good clinical performance and no need of steroid treatment for symptom relief constitute better preconditions for application of potentially aggressive salvage regimens. Younger patients amenable to high-dose chemotherapy with autologous stem cell transplantation (HDAST) for salvage treatment carry the best prognosis.[3] In patients who do not qualify for more aggressive regimens, rituximab, temozolomide, topotecan, and other agents may be considered.[4]

In this issue Tabouret and coworkers[5] report on neuroimaging findings in 85 patients who had been enrolled in a prospective clinical trial for elderly patients with PCNSL.[6] Sixty-nine of those 85 patients suffered from a relapse, with 52 of them having relapse in the brain. Notably, at initial diagnosis 16 of the 85 patients showed nonenhancing lesions distant from the enhancing tumor site, which decreased in size by more than 50% under tumor-directed therapy and strongly suggested that those lesions represented nonenhancing tumor. An impressive example of such a T2-FLAIR lesion and its shrinkage under therapy is depicted in Figure 2 of this paper.[5] Now, of those 16 patients 10 relapsed, five among those showing relapse within the non-enhancing (tumorous) shrinking lesions under therapy. This is in contrast to our usual perception of this disease. On MRI, tumor manifestations in PCNSL most frequently present as intensively enhancing unifocal or multifocal lesions and are characteristically located in close vicinity to the ventricles.[7] Accordingly, the IPCG consensus[2] defined treatment response criteria based on MRI with an exclusive focus on enhancing lesions: complete response (CR) is categorized as disappearance of all enhancing lesions, partial response (PR) as a shrinkage of those by ≥50%, progressive disease (PD) as growth of enhancing lesions by ≥25%, and stable disease (SD) as any other situation. A peculiarity of PCNSL is the observation that despite successful treatment, some patients show small but persistent enhancing abnormalities in the location of the original tumor or biopsy, which might shrink or disappear during follow-up without any further treatment, and are therefore categorized as unconfirmed complete response (CRu).[2]

Nonenhancing lesions at primary diagnosis[7] and at relapse[8] are considered exceptional, but they may be more frequent according to the result of Tabouret's study. The authors conclude that—in addition to typical enhancing lesions—T2-FLAIR hyperintense lesions without contrast enhancement may constitute additional foci of disease that require attentive follow-up and potentially constitute sites of disease relapse. Thus, surveillance in PCNSL patients with regular MRI follow-up may become more demanding and interpretation of those images more complex; the median age of patients with newly diagnosed PCNSL is >60 years,[4] and this population harbors the risk of developing new hyperintense T2-FLAIR lesions completely unrelated to tumor such as white matter lesions of vascular pathology.

Since T2-FLAIR lesions might represent tumor, they are targets of tumor-directed therapy. Since they might be an origin of recurrence, do we have to further redefine the usual response criteria[2] by inclusion of T2-FLAIR sequence assessments, as Tabouret and coworkers recommend? This would

be difficult since it has not been shown in large patient cohorts that a definite separation of tumor T2-FLAIR lesions from other pathology can be achieved reliably with other imaging modalities such as F-18-labeled fluordeoxyglucose (FDG) positron emission tomography (PET)[9] or MR spectroscopy.[10] For practical reasons, however, such an extension of response criteria to these T2-FLAIR lesions seems unnecessary since no case with only nonenhancing relapse has been identified in the series by Tabouret and coworkers.[5] Nevertheless, their observation is of clinical relevance, and we should closely monitor suspicious foci of nonenhancing lesions that increase in size at regular MRI follow-up, particular;y if those lesions had shown shrinkage under first-line therapy.

Conflict of interest statement. None declared.

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