Histopathological variation in the demyelinating sentinel lesion of primary central nervous system lymphoma

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INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an extranodal non-Hodgkin's lymphoma confined to the brain, leptomeninges, and the spinal cord.[10] It is a rare disease, accounting for 3% of all primary brain tumors and 4–6% of all extranodal lymphomas.[9,14] Most patients with PCNSL present initially with histological features of diffuse large B cell lymphoma (DLBCL). However, in rare instances, a patient can experience an atypical course with the initial biopsy suggesting the presence of demyelination;[4,10] in most of these cases, perivascular infiltration of inflammatory cells is a distinctive feature identified during histological analysis. A few patients show parenchymal infiltration instead of perivascular infiltration, but no patients have both of these features in combination.
A review of the literature revealed only eleven cases of demyelinating sentinel lesions in PCNSL have been reported to date [Table 1]. Among them, six presented with perivascular infiltrative inflammatory cells during histological analysis,[1,5,8,11,12,15] and four had parenchymal infiltration instead of perivascular infiltration.[1,6,7,10] The remaining patient had partial demyelination with perivascular and intraparenchymal infiltration of T lymphocytes.[10] All of the patients underwent repeated histological examinations to confirm the final diagnosis of PCNSL. All of the patients were considered to be immunocompetent, and one patient was reported to experience spontaneous regression of the sentinel lesion without steroid therapy.[10]

Here, we present the oldest patient with a completely demyelinating sentinel lesion reported to date, who had the distinct histology of combined perivascular and parenchymal infiltration of inflammatory cells (T lymphocytes and macrophages). The sentinel lesion we describe also had spontaneous regression without steroid therapy.

**CASE PRESENTATION**

A 78-year-old female initially presented to a local hospital with a history of fall, sustaining a contusion in the right temporoparietal region. Her neurological examination revealed weakness of the left lower limb and cognitive dysfunction. The head computed tomography (CT) scan showed minimal bilateral intraventricular and right occipital subarachnoid hemorrhage, as well as incidental hyperdense lesions in the corpus callosum, cingulate gyrus, left frontal, and right periventricular regions, for which she was referred to our center. Post-contrast T1-weighted magnetic resonance (MR) imaging revealed that all the hyperdense lesions identified on CT were enhanced, in addition to newly identified lesions in the left occipital lobe and the midbrain, the latter of which was compressing the sylvian aqueduct. The lesion around the corpus callosum showed homogeneous enhancement [Figure 1a and b], with a high signal on diffusion-weighted imaging [Figure 1c] and a low apparent diffusion coefficient (ADC) value [Figure 1d]. MR spectroscopy of the same lesion revealed increased lipids with elevated choline, creatine, and N-acetylaspartate peaks. The lesion in the left occipital lobe showed heterogeneous enhancement with a partial open-ring pattern and low ADC value [Figure 1b and d] which was chosen for a stereotactic biopsy due to its accessible nature and comparatively safer location. On the 5th day post-biopsy, repeated imaging showed significant regression of all the lesions without steroid therapy [Figure 1e].

The histopathological report from this biopsy described perivascular and parenchymal lymphocytic infiltration with the presence of large diffuse astrocytes as well as foam cells, and evidence of astrogliosis [Figure 2a]. Further,
Table 1: A summary of the literature on the histopathology of demyelinating sentinel lesions in primary central nervous system lymphoma.

| First author and year of publication | Age / Sex | First biopsy | Histopathological findings of inflammatory cells | Diagnosis | Spontaneous regression* without steroid therapy | Final diagnosis (DLBCL) |
|--------------------------------------|-----------|--------------|--------------------------------------------------|-----------|-----------------------------------------------|------------------------|
| Kwarta et al. 2016^8                  | 57 F      | NF stain: acute multifocal demyelination with axonal preservation | Reactive perivascular astrocytosis and macrophages | Tumefactive MS or ADEM | Absent | PCNSL* |
| Kalus et al. 2016^5                   | 26 F      | Inflammatory demyelination | Perivascular cuffs of lymphoid cells | Tumefactive demyelination | Absent | PCNSL** |
| Ohe et al. 2013^12                    | 72 M      | KB stain: severe myelin loss | Perivascular lymphocytes and foamy macrophages | Tumefactive MS | Absent | PCNSL** |
| Ng et al. 2007^11                     | 29 F      | LFB stain: extensive myelin destruction | Perivascular cuffing of lymphocytes | Pseudotumoral MS | Absent | PCNSL** |
| Alderson et al. 1996^13               | 58 F      | Demyelination with axonal sparing | Perivascular T and few B cells | Chronic inflammatory demyelination | Absent | PCNSL** |
| Yamamoto et al. 2014^12               | 70 M      | Myelin destruction with sparing of axon | Focal Perivascular aggregation of lymphocytes | MS | Absent | PCNSL** |
| Lu et al. 2016^10                     | 44 F      | NF and LFB stain: loss of both myelin and axons | Infiltration of inflammatory cells with macrophages | Inflammation with partial demyelination | Present | Biopsy and autopsy PCNSL** |
| Kuhlmann et al. 2001^16               | 65 M      | LFB stain: demyelinating lesion | Infiltration of macrophages and T cells | MS | Absent | PCNSL** |
| Alderson et al. 1996^13               | 57 F      | LFB stain: the destruction of myelin with axonal sparing | Many T lymphocytes and foamy macrophages | MS | Absent | PCNSL** |
| Kuroda et al. 1992^7                  | 56 F      | Inflammatory demyelination | Infiltration of lymphocytes and reactive astrocytosis | MS | Absent | PCNSL** |
| Husseini et al. 2012^20               | 59 F      | SBB stain: nearly complete loss of myelin | Perivascular and intraparenchymal T lymphocytes | Inflammatory demyelinating disease | Absent | PCNSL** |
| Present case                           | 78 F      | KB stain: demyelination | Virchow-Robin perivascular space and parenchymal infiltration of lymphocytes and macrophages | Tumefactive MS | Present | PCNSL** |

ADEM: Acute disseminated encephalomyelitis, DLBCL: Diffuse large B cell lymphoma, F: Female; KB: Klüver-Barrera, LFB: Luxol fast blue, M: Male; MS: Multiple sclerosis; NF: Neurofilament, PCNSL: Primary central nervous lymphoma, SBB: Sudan Black B. *Biopsy from the same site, **Biopsies from different sites, *Of the sentinel lesion.
immunostaining for macrophage-specific markers described an abundance of CD68-positive histiocytes [Figure 2b]; there were also abundant CD3-, CD4-, and CD8-positive reactive T-lymphocytes [Figure 2c] with a small number of CD20- and CD79a-positive B lymphocytes [Figures 2d and e, respectively] in the perivascular and/or parenchymal lesions. Klüver–Barrera (KB) staining showed a reduced uptake of staining, suggestive of demyelination [Figure 2f]. The absence of evidence of monoclonality in the biopsy specimens indicated non-neoplastic changes. Thus, based on the histopathological report, the patient was diagnosed with tumefactive multiple sclerosis (MS). She was then treated with a short-course of intravenous methylprednisolone and was discharged without a neurological deficit.

She remained relatively stable for a period of almost 3 months after the initial biopsy but was subsequently re-admitted with progressive disorientation. Post-contrast T1-weighted MR imaging showed gliosis and complete resolution of the previously biopsied lesion in the left occipital lobe [Figure 3a], while all the other residual lesions had enlarged with progressive homogeneous enhancement [Figure 3a-c] and low ADC value [Figure 3d]. An accessible lesion located within the ventricle on the contralateral hemisphere to the previous biopsy site was biopsied promptly through an endoscopic-guided approach. The histopathological report revealed diffuse lymphoid atypical cells [Figure 3e]. Immunostaining was positive for the B cell marker CD20 [Figure 3f]. This confirmed the diagnosis of PCNSL of the DLBCL subtype. The MR spectroscopy was also suggestive of PCNSL with a high lipid peak. She was treated with a high dose of methotrexate chemotherapy and experienced an improved clinical course with a better radiological response.

DISCUSSION

Intracerebral demyelinating lesions that appear before the true diagnosis of PCNSL are rare, when detected initially in non-neoplastic lesions they are described as a "sentinel lesion"[1,4] The term "sentinel lesion" was coined in 1996 by Alderson and it has subsequently been used multiple times by different scholars.[1] The sentinel lesion demonstrates T2 hyperintensity with various degrees of contrast enhancement over time, and it is associated with a diverse histological picture that mostly gives inconclusive results.[1,4] Furthermore, in some instances distinguishing tumefactive MS for sentinel lesion of PCNSL is difficult on the radiological study. The heterogeneity of ADC values that increased with myelin destruction and vasogenic edema and that reduced with the infiltration of inflammatory cells makes differentiation more challenging.[2]

Several hypotheses have been proposed regarding the pathophysiology of sentinel demyelinating lesions. Kuhlmann et al. noted anti-myelin oligodendrocyte glycoprotein antibody in the serum of PCNSL patients before sentinel demyelination, and explained these antibodies may have been produced by a monoclonal population of transformed B cells, resulting in autoimmune demyelination.[6] Later, Kvarta et al. further described this process as a paraneoplastic phenomenon.[8] Notably, however, the association of other well-recognized paraneoplastic antibodies such as anti-Hu, -Yo, or -Ri in patients with sentinel lesions and PCNSL is unclear.[4] Another proposed hypothesis describes how sentinel lesions may express an immune response against the developing PCNSL, which only manifests when a subclone evades the immune system.[3,14] Two of the reports also suggested that the sentinel lesion could represent the initial immunological response against the developing PCNSL.[3,10]
Histologically, the sentinel lesion is mostly composed of either perivascular or parenchymal infiltration of inflammatory cells and is frequently accompanied by demyelination. Usually, CD3-positive T lymphocytes predominantly possess perivascular cuffing, and in a few cases, infiltration of T lymphocytes is limited to the parenchymal cells alone. Our patient was unique due to the presence of both perivascular and parenchymal lymphocytes. A similar finding was also observed by Husseini et al., but our patient is particularly unique due to the presence of complete demyelination on KB staining. To the best of our knowledge, none of the cases of complete demyelinating sentinel lesions reported to date describe the presence of perivascular and parenchymal infiltration of inflammatory cells at the same time. The reason behind this distinct histological picture is unknown. The unique feature of spontaneous regression in an immunocompetent patient without steroid therapy, and with predominant T cells, advocates the potential presence of a suppressive cell-mediated anti-tumor response.

CONCLUSION

The sentinel lesion of PCNSL in immunocompetent patients expresses a variable histological pattern of inflammatory cells. The usual perivascular infiltrative pattern is commoner than parenchymal infiltration, and the mixed-pattern involving both perivascular and parenchymal infiltration is exceptionally rare. This case report describes a unique histological finding and describes the recognized variations in sentinel lesion histopathology. Moreover, distinguishing tumefactive MS for sentinel lesion of PCNSL is difficult on radiological study alone. Hence, the accurate diagnosis and treatment of PCNSL require repeated biopsies for histopathological examinations.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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