

# Neuroimaging of Primary Central Nervous System Lymphoma in Immunocompetent Patients: Comparison of Recent and Previous Findings

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## Abstract

The typical neuroimaging features of primary central nervous system lymphoma (PCNSL) have been described as single or multiple intra-axial, homogenous, contrast-enhancing lesions with marked perilesional edema and restricted diffusion, usually contacting the cerebrospinal fluid surface. Necrosis, peripheral enhancement, hemorrhages, and calcifications are unusual. Recently, some of our patients with PCNSL have had atypical neuroimaging features even before treatment. In this article, we review the neuroimaging characteristics of PCNSL in immunocompetent patients and analyzed how imaging findings over the last 10 years differ from those from more than 10 years ago. Neuroimaging findings suggest that PCNSL is a disease that affects the entire brain. Although some imaging findings are characteristic of PCNSL, the frequency of atypical findings on conventional neuroimaging is increasing. Atypical neuroimaging findings do not rule out PCNSL, even in immunocompetent patients.

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**Key words:** primary central nervous system lymphoma, neuroimaging, atypical feature, diagnosis

## Introduction

Primary central nervous system lymphoma (PCNSL) represents up to 3.1% of all primary central nervous system malignancies<sup>1</sup>. In nearly all PCNSLs are diffuse large B-cell lymphomas, with T-cell

lymphomas being rare. Imaging findings vary with the immune status of the patient. Most PCNSLs are diagnosed in patients aged 45 to 70 years, with a mean age in the 6th or 7th decade. A slight male predominance has been reported in Japan<sup>1</sup>.

The typical neuroimaging features of PCNSL have been described previously<sup>2-4</sup>. These features include

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single or multiple intra-axial, homogenous, contrast-enhancing lesions with marked perilesional edema and restricted diffusion, usually contacting the cerebrospinal fluid surface. Necrosis, peripheral enhancement, hemorrhages, and calcifications are unusual, and other diagnoses should be considered if any of these features are present. If neuroimaging findings are characteristic of PCNSL, the diagnosis is not difficult. However, neuroimaging findings can be atypical in patients who are immunodeficient or who have been treated with radiation, antineoplastic agents, or steroids. Moreover, in recent years, atypical neuroimaging features have sometimes been obtained in immunocompetent patients, even before treatment. Furthermore, in 5% of patients with PCNSL, neuroimaging findings are completely normal<sup>56</sup>. In this article, we review the neuroimaging characteristics of PCNSL in immunocompetent patients and discuss the differences between imaging findings over the last 10 years and those from more than 10 years ago.

## Review

### Computed Tomography

On computed tomography (CT) the lesions of PCNSL are typically (86% to 92% of cases) isodense to hyperdense<sup>4</sup>. Densely packed abnormal cells are thought to be responsible for the hyperdensity<sup>7-11</sup>. In general, the mass effect is not as prominent as might be expected on the basis of the size of the lesion. On neuroimaging, PCNSLs typically manifests as intra-axial lesions of the cerebral hemispheres (20% to 43%), thalamus and basal ganglia (13% to 20%), corpus callosum (14%), ventricle wall and choroid plexus (12%), and cerebellum (9% to 13%)<sup>12,13</sup>. Posterior fossa involvement is seen in 10% to 24% of cases<sup>2,14</sup>. In 65% to 80% of cases, lesions are solitary and tend to be large, with a mean diameter of 35 to 39 mm<sup>13-16</sup>. Multiple lesions are not uncommon (20% to 35%) but tend to be small (mean diameter, 16.4–22 mm)<sup>13-16</sup>. In cases with multiple lesions, at least 1 lesion is typically observed in deep structures, including the basal ganglia and thalamus<sup>2,11,17</sup>. The highest reported number of lesions is 8<sup>3</sup>. Edematous changes are generally severe in the white matter

but are mild in the basal ganglia and posterior fossa<sup>14</sup>. In 12% of cases, edema is absent<sup>13</sup>. Lesions near the brain surface typically invade the dura and falx, and, thus, neuroimaging findings resemble those of meningioma. Because lesions at the cerebellopontine angle are generally not accompanied by edema, they mimic schwannomas or meningiomas<sup>9,13</sup>. Necrosis and a cystic appearance are uncommon features of untreated PCNSL in immunocompetent patients<sup>2,13</sup>. Cysts, when present, are usually small (mean diameter, 3 mm) and single<sup>2,14</sup>.

Contrast enhancement is typically homogenous (71%) and strong (88%)<sup>3,4,11,13</sup>. Ring enhancement is usually associated with necrosis and is present in only 5.3% to 17% of immunocompetent patients<sup>3,18,19</sup>. The enhancing ring wall is quite thick, and the center shows isodensity instead of hypodensity. Enhancement is absent in only 2% of cases<sup>7,18</sup>. The degree of enhancement is thought to correlate positively with the sensitivity to chemotherapy.

In immunodeficient patients, including those with acquired immune deficiency syndrome (AIDS), PCNSLs are often multifocal<sup>20</sup>. The basal ganglia and corpus callosum are more frequently involved than in patients without AIDS<sup>18-20</sup>. Precontrast CT usually shows a low-density lesion, and ring-like enhancement is present in up to 75% of cases<sup>7,12,20</sup>. The center of the ring is hypodense<sup>7,12,20</sup>. Twelve percent of cases show no enhancement<sup>21</sup>. Spontaneous hemorrhages of PCNSL lesions are frequent in immunodeficient patients<sup>20</sup>.

### Magnetic Resonance Imaging

When PCNSL is suspected, contrast-enhanced T1-weighted magnetic resonance imaging (MRI) is the imaging technique of choice<sup>12,22,23</sup>. On precontrast T1-weighted images lesions are usually isointense or hypointense<sup>7,11,24</sup>. We were able to observe the area of origin on MRI, and most cases show at least 1 intra-axial lesion contacting a cerebrospinal fluid surface (either subarachnoid or intraventricular)<sup>7,13,25-27</sup>. Lesions not in contact with the subarachnoid space are low-grade PCNSL<sup>28</sup>. Strong homogenous enhancement is often present in PCNSL<sup>2-4,13,29</sup>. The degree of enhancement correlates positively with

the size of the lesion<sup>3</sup>. Some cases (0% to 13%) show ring enhancement, and a few cases show open-ring enhancement and a “notch sign”, which is a deep, abnormal depression at the tumor margin<sup>14</sup>. When present, rings are usually thicker and less uniform than those in cases of demyelination. Rare cases (0% to 1%) without enhancement have been described<sup>36</sup>, usually in the setting of low-grade disease<sup>28</sup> or intravascular lymphomatosis (cerebral manifestation of a systemic disease)<sup>30</sup> in immunocompetent patients. Infiltration of the corpus callosum is commonly regarded as the most characteristic sign of PCNSL. Symmetrical lesions involving the genu or splenium of the corpus callosum are referred to as a “mirror pattern” or “butterfly pattern”. PCNSLs tend to show subependymal and leptomeningeal spread (97% of cases)<sup>4,13,15,31</sup>. Linear enhancement along perivascular spaces is highly suggestive of PCNSL<sup>9,27,29,31</sup>, because PCNSL has an affinity for perivascular extension. After steroids are administered, lesions visualized with MRI can disappear in as little as several hours<sup>32</sup>. Corticosteroids can decrease the area of gadolinium enhancement. With effective treatment, areas of enhancement become smaller and weaker and finally disappear<sup>7,33</sup>. The area of enhancement usually appears wider on MRI than on CT. A lesion shown with CT with contrast enhancement to be a solitary may sometimes be shown with MRI to be multiple lesions. When steroids are administered, 40% of individual lesions become smaller, and necrosis may be observed on neuroimaging<sup>7</sup>. Complete remission is sometimes observed<sup>32</sup>. Usually, PCNSL lesions grow rapidly if left untreated. However, some lesions, called vanishing tumors, can disappear spontaneously. About half of vanishing tumors are PCNSLs<sup>32,34</sup>.

The eye is involved in 20% to 25% of patients with PCNSL<sup>15,35,36</sup>. Ocular lymphomas should be diagnosed with contrast-enhanced MRI, although doing so can be difficult<sup>37</sup>. Instead, ocular lymphoma can be diagnosed with cytologic examination of vitreal aspirate or slit-lamp examination. On MRI, ocular lymphoma can manifest as nodular enhancing lesions in the macula or thickening of the uvea<sup>7,13,37</sup>.

On T2-weighted images lesions are usually

isointense or hyperintense (**Fig. 1C**), but characteristics can vary. For example, 40% of lesions on T2-weighted images show hypointensity<sup>4,13,18</sup>, which is attributed to high cellular density of the tumor<sup>7,18</sup>. Areas with tumor infiltration and edema also exhibit hyperintensity. Peritumoral edema is usually present but is less prominent than in malignant gliomas or metastases<sup>18,25,38</sup>. Six percent of PCNSL lesions do not show edema<sup>14,21</sup>. Edema is thought to be of vasogenic origin<sup>7</sup>. In some suprasellar PCNSLs, edema-like changes occur along the optic tract and are thought to be due to dilated perivascular spaces<sup>39</sup>. Hemorrhages and calcifications are unusual before radiotherapy or chemotherapy<sup>2,18</sup>.

On fluid-attenuated inversion recovery (FLAIR) imaging, both tumors and areas of edema appear hyperintense<sup>7</sup>. Therefore, the spread of tumor and edema is easily detected with FLAIR imaging. A characteristic finding is bilateral symmetrical hyperintensity with subependymal extension<sup>13,16</sup>. Although lesions shrink after treatment, areas of hyperintensity usually persist, regardless of the presence of tumor<sup>7</sup>.

Because diffusion is usually restricted within lymphomas owing to high cellular density, hyperintensity on diffusion-weighted images (DWIs) and hypointensity on apparent diffusion coefficient (ADC) maps<sup>7,9,40,41</sup> are usually seen. PCNSL lesions often have lower ADC values ( $0.51\text{--}0.63 \times 10^{-3} \text{ mm}^2/\text{s}$ ) than do high-grade gliomas ( $0.75\text{--}0.96 \times 10^{-3} \text{ mm}^2/\text{s}$ ) or metastases ( $0.68 \times 10^{-3} \text{ mm}^2/\text{s}$ )<sup>7,40,42</sup>. Measurements before treatment of ADC in enhancing regions in patients with PCNSL are predictive of clinical outcome<sup>43</sup>. When treatment is effective, ADC findings normalize within several days<sup>7,44</sup>. Thus, repeated ADC measurements can be used as markers of therapeutic response.

On perfusion-weighted images PCNSL shows low cerebral blood volume (CBV)<sup>40</sup>. The maximum relative CBV in tumor tissue, calculated as a ratio of CBV in contralateral normal-appearing white matter, is typically lower in lymphomas (1.10–2.33) than in high-grade gliomas (5.76–6.33) or metastases (4.55–5.27)<sup>40,45,46</sup>.

On susceptibility-weighted images, there are no particular or specific characteristics and no

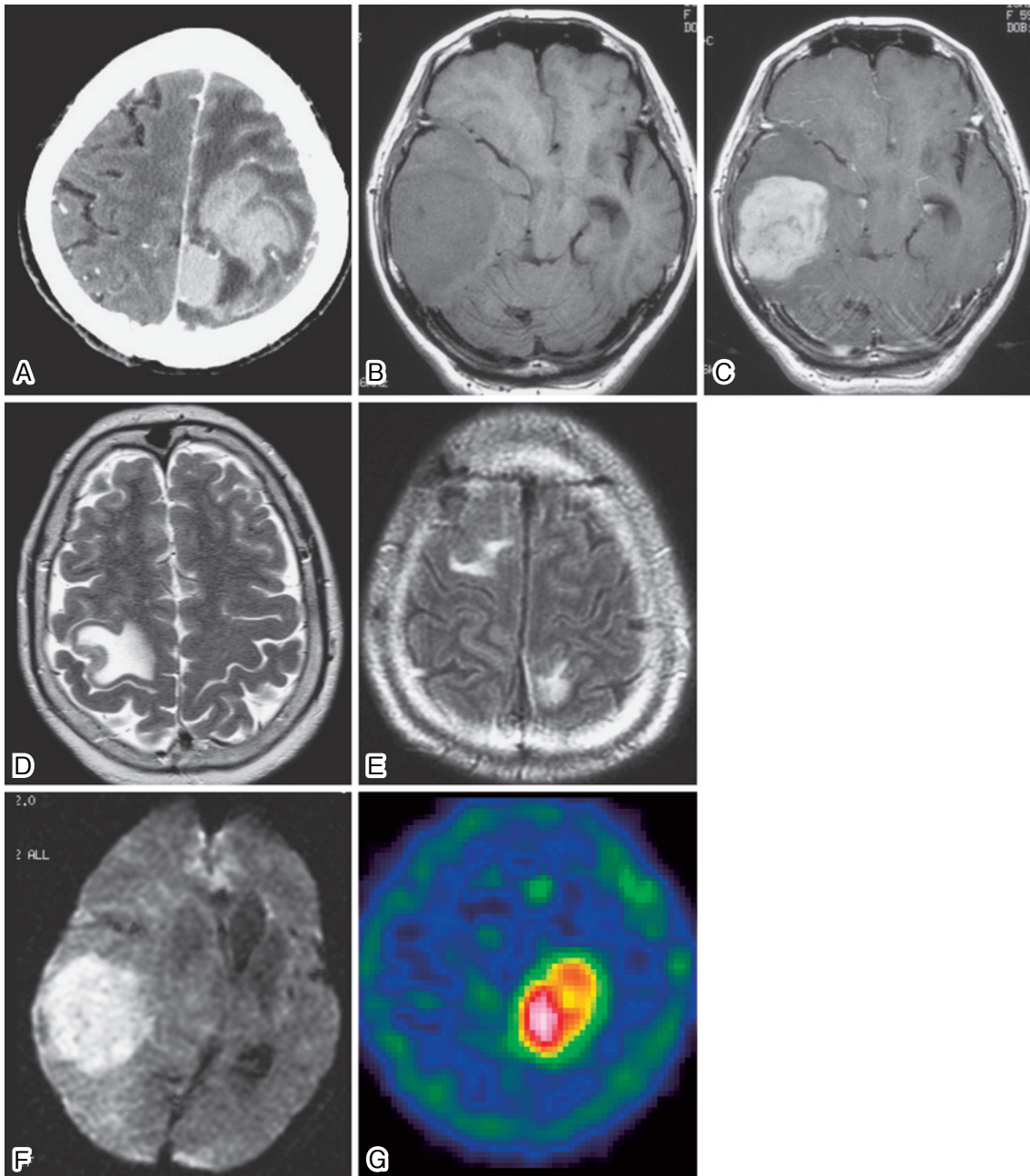


Fig. 1 Typical neuroimaging findings  
 A) 68-year-old woman, enhanced CT  
 B) 59-year-old woman, MRI T1-weighted image.  
 C) 59-year-old woman, MRI enhanced T1-weighted image.  
 D) 72-year-old woman, MRI T2-weighted image.  
 E) 50-year-old man, MRI FLAIR image.  
 F) 59-year-old woman, MRI DWI.  
 G) 67-year-old woman, TICI SPECT delayed image.

microhemorrhages or calcifications, which are frequently seen in high-grade gliomas<sup>47</sup>.

Proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) provides metabolic information. In PCNSL, an almost complete loss of n-acetyl aspartate, a decrease in creatine, a great increase in choline, and an increase

in lactate (90%) are observed and are similar to the changes observed in malignancy<sup>48,49</sup>. A reported hallmark of PCNSL on MRS is lipid peaks (90%) much higher than those in glioblastoma (14%)<sup>41,49,50</sup> and high choline/creatine ratios (>3)<sup>3,7</sup>. Of these findings, high levels of lipids and lactate indicate a

poor prognosis<sup>50</sup>.

### Angiography

Cerebral angiography, although rarely performed to diagnose PCNSL, yields characteristic findings. For example, PCNSL appears as an avascular space-occupying lesion with a mass effect (61% to 70%)<sup>17,19</sup>. In 30% to 39% of cases, tumor staining is present but weak<sup>17,19</sup>. Tumor staining appears during the late arterial or capillary phase and is diffuse and homogenous. Tumor neovascularity with irregular walls is observed in 3% to 14% of cases, arteriovenous shunting in 0% to 5%, and arterial encasement in 3% to 14%<sup>17,51</sup> of cases. Dural arterial supply is observed in 0% to 10% of cases<sup>17,25</sup>.

### Nuclear Imaging

N-isopropyl [<sup>123</sup>I]-p-iodoamphetamine (IMP) single-photon emission CT (SPECT) shows retention in delayed images<sup>52</sup>. On delayed SPECT images the IMP index is 7 in cases of PCNSL but is less than 1 in cases of malignant glioma<sup>52</sup>. High IMP index of PCNSL is similar to that of malignant melanoma<sup>53</sup>.

With <sup>201</sup>TlCl-SPECT, homogeneously enhancing abnormalities are usually observed<sup>54</sup>.

With <sup>67</sup>Ga scintigraphy, accumulation is observed 72 hours after injection. The sensitivity of <sup>67</sup>Ga scintigraphy is reported to be 83.1%<sup>55</sup>.

<sup>18</sup>Fluorodeoxyglucose (FDG)-positron emission tomography (PET) in cases of PCNSL reveals hypermetabolic lesions with increased uptake of FDG (86%)<sup>7,9,56</sup>, as is seen in malignant gliomas. After effective chemotherapy, FDG uptake disappears, and thus, FDG-PET can be used to evaluate the early therapeutic response<sup>56</sup>. After steroid treatment, the degree of hypermetabolic activity in PCNSL may decrease<sup>57</sup>.

On <sup>11</sup>C-methionine-PET, uptake is extremely high. The area of increased uptake is often larger than the enhancing lesion on MRI<sup>58</sup>. The area and degree of methionine accumulation in the tumor tissue decrease after radiation therapy<sup>58</sup>.

In these nuclear images, immunodeficient patients with PCNSL show characteristics similar to those of immunocompetent patients. Neuroimaging findings facilitate differential diagnosis from infectious

diseases<sup>54,59-61</sup>.

### Materials and Methods

We reviewed pretreatment neuroimages, including MRIs, of patients with PCNSL of the diffuse large B-cell lymphoma subtype confirmed with biopsy, cytology, or autopsy from 1990 through 2012 at our institution. We included only immunocompetent patients who did not have human immunodeficiency virus infection. Patients with systemic malignant lymphoma disease, intravascular lymphomatosis, or meningeal lymphomatosis were excluded from evaluation. The patients were divided into 2 groups: late group included patients diagnosed between 2003 and 2012, and early group included patients diagnosed between 1990 and 2002. Late group comprised 19 women and 21 men aged 48 to 82 years (mean age, 63.8 ± 9.7 years) at the time of diagnosis. Early group comprised 18 women and 24 men aged 22 to 85 years (mean age, 62.7 ± 10.1 years).

All scans were reviewed according to the location of the lesion (including deep or superficial locations in the brain), size, margin, and signal density/intensity characteristics. The presence of calcifications, cystic or necrotic changes, hemorrhages, and enhancement characteristics were also examined.

Statistical analysis was performed with the chi-square test. A p-value less than 0.05 was considered to indicate statistical significance.

### Results

#### CT

On CT, PCNSL lesions were isodense to hyperdense in 93% of patients in late group and 92% of patients in early group. Lesions were located in the cerebral hemisphere (45% in late group, 42% in early group), thalamus and basal ganglia (22% in late group, 20% in early group), corpus callosum (11% in late group, 10% in early group), ventricle wall and choroid plexus (7% in late group, 10% in early group), and cerebellum (15% in late group, 18% in early group). Posterior fossa involvement was seen

in 16% of patients in late group and 19% in early group. Eighty percent of patients in late group and 75% in early group had solitary lesions, with a mean diameter of 29 mm ( $p < 0.05$ ) in late group and 37 mm in early group. Multiple lesions were observed in 28% of patients in late group and 22% in early group, and the mean diameter was 17 mm in late group and 20 mm in early group. The highest number of lesions was 5 in late group and 4 in early group. No edema was seen in 3% of patients in group A and 2% in group B. Necrosis was observed in 1% of patients in late group and 1% in early group, and a cystic appearance was seen in 3% of patients in late group and 5% in early group.

Homogenous enhancement was observed in 65% ( $p < 0.05$ ) of patients in late group and 80% in early group (**Fig. 1A**). Strong enhancement was observed in 84% ( $p < 0.05$ ) of patients in late group and 91% in early group (**Fig. 1A**). Ring enhancement was present in 17% ( $p < 0.05$ ) of patients in late group and 7% in early group. In a 67-year-old woman (**Fig. 2A**), the enhancing ring wall was thick, and the center was isodense rather than hypodense. No enhancement was noted in 1% of patients in late group and 1% in early group.

### MRI

In 93% of patients in late group and 98% in early group, lesions were isointense or hypointense on precontrast T1-weighted images (**Fig. 1B**). Ninety-four percent of patients in late group and 97% in early group showed at least 1 intra-axial lesion contacting a cerebrospinal fluid surface. Lesions not in contact with the subarachnoid space were observed in 6% of patients in late group and 3% in early group. Strong homogenous enhancement was present in 72% ( $p < 0.05$ ) of patients in late group and 89% in early group (**Fig. 1C**). Fifteen percent ( $p < 0.05$ ) of patients in late group and 5% in early group showed ring enhancement (**Fig. 2B**), and a few patients showed open-ring enhancement (2% of patients in late group, 2% in early group) and a “notch sign” (4% of patients in late group, 2% in early group). One percent of patients in late group and no patients in early group showed no enhancement. A “mirror pattern” was observed in

9% of patients in late group and 8% in early group. Subependymal and leptomeningeal spread was observed in 90% of patients in late group and 88% in early group. The eye was involved in 5% of patients of late group and 4% in early group.

Lesions were usually isointense or hyperintense on T2-weighted images (**Fig. 1D**), although hypointensity on T2-weighted images was observed in 55% ( $p < 0.01$ ) of patients in late group and 23% in early group (**Fig. 2C**). Edema-like changes along the optic tract were not observed in either group.

FLAIR showed hyperintensity in 70% ( $p < 0.05$ ) of patients in late group and 92% in early group (**Fig. 1E**). Some patients showed hypointensity (**Fig. 2D**).

Hyperintensity on DWI was observed in 85% ( $p < 0.05$ ) of patients in late group and 96% in early group (**Fig. 1F**), and hypointensity on ADC maps was seen in 85% ( $p < 0.05$ ) of patients in late group and 96% in early group. Some patients did not show DWI hyperintensity (**Fig. 2E**).

In late and early groups, respectively, <sup>1</sup>H-MRS showed complete loss of n-acetyl aspartate in 85% and 67% of patients, a decrease in creatine in 90% and 100%, a marked increase in choline in 85% and 67%, an increase in lactate in 90% and 67%, markedly elevated lipid peaks in 90% and 67%, and high choline/creatinine ratios ( $> 3$ ) in 90% and 67%.

### Angiography

Cerebral angiography showed an avascular space-occupying lesion with a mass effect in 88% of patients in late group and 78% in early group. Tumor staining was observed in 12% of patients in late group and 22% in early group. In late and early groups, respectively, the rates of tumor neovascularity with irregular walls were 6% and 10%, of arteriovenous shunting were 0% and 5%, of arterial encasement were 0% and 5%, and of dural arterial supply were 6% and 5%.

### Nuclear Imaging

Delayed images of IMP-SPECT showed retention in 86% of patients in late group and 86% in early group. With <sup>201</sup>Tl-SPECT, homogeneously enhancing abnormalities were observed in 94% of patients in late group and 86% in early group (**Fig. 1G**).

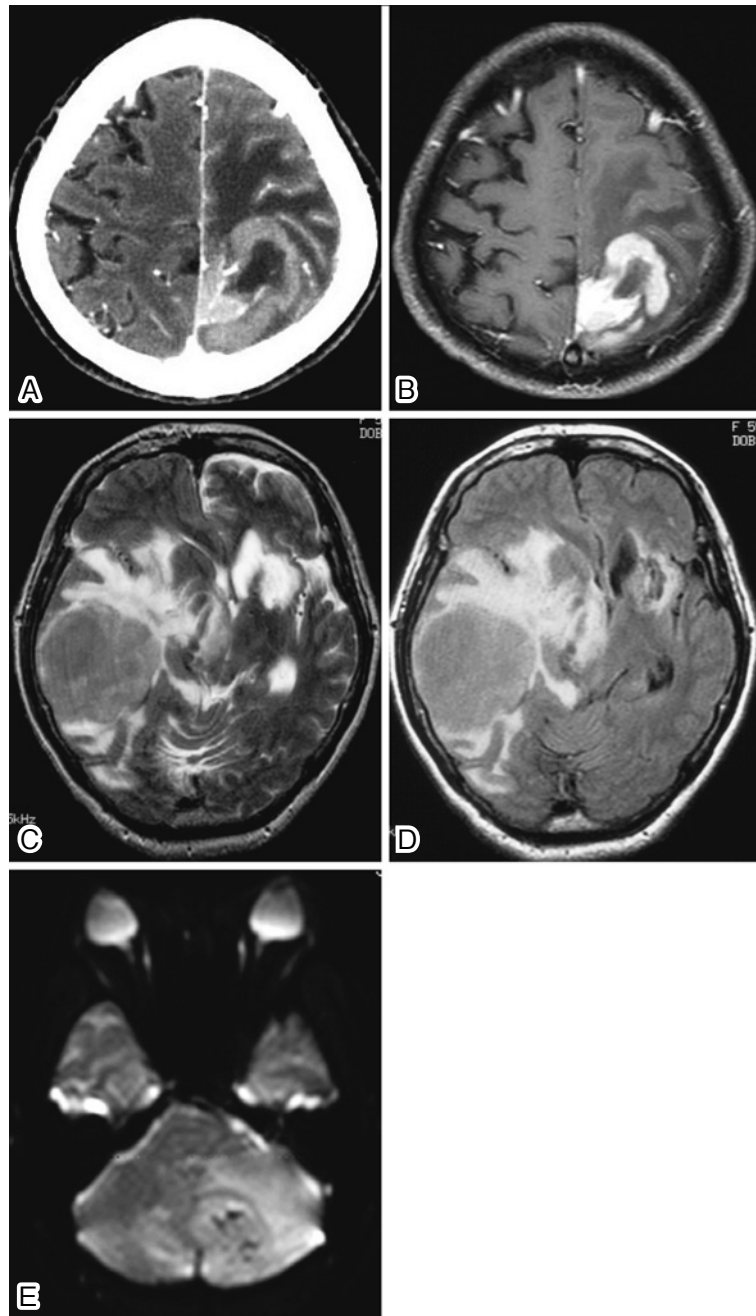


Fig. 2 Atypical neuroimaging findings

- A) 67-year-old woman, enhanced CT
- B) 67-year-old woman, MRI enhanced T1-weighted image.
- C) 59-year-old woman, MRI T2-weighted image.
- D) 59-year-old woman, MRI FLAIR image.
- E) 50-year-old man, MRI DWI

With  $^{67}\text{Ga}$  scintigraphy, positive accumulation was observed in 86% of patients in late group and 67% in early group.

$^{18}\text{F}$ FDG-PET revealed hypermetabolic lesions in 90% of patients in late group but was not performed for early group.  $^{11}\text{C}$ -methionine-PET showed high uptake in 100% of patients in late group but was not

performed for early group.

### Discussion

According to the findings in the literature and our results, in neuroimaging of PCNSL, 1) a mass effect was not prominent, 2) multiple lesions were not

uncommon, 3) the central structure was affected, 4) necrosis and cysts were uncommon, 5) enhancement was homogenous, 6) lesions grew rapidly, 7) CVB in perfusion-weighted images was low (because the reference is the contralateral normal-appearing white matter), and 8) enhanced areas regressed rapidly after treatment. These characteristics suggest that visible enhancing lesions are only a part of PCNSL, which may be a whole-brain disease. This idea is also supported by microscopic studies<sup>6,8</sup>.

The typical neuroimaging features of PCNSL are single or multiple homogenous intra-axial lesions showing isodensity to hyperdensity on CT, isointensity to hypointensity on MRI T1-weighted images, isointensity to hyperintensity on T2-weighted images, hyperintensity on FLAIR images, and hyperintensity on DWI. The lesions sometimes show peritumoral edema and contact cerebrospinal fluid surfaces. Enhancement is typically homogenous and strong, and necrosis, hemorrhages, and calcifications are unusual.

Atypical CT and MRI findings include heterogeneous and weak or ring enhancement and hypointensity on T2-weighted images and isointensity to hypointensity on FLAIR imaging and DWI. Atypical neuroimaging findings in immunocompetent patients with PCNSL are now frequently obtained and resemble findings in patients with AIDS. Although the greater frequency of atypical findings may be attributed in part to advances in diagnostic equipment or skills, other factors may be involved. However, the cause of the increasing frequency of atypical CT and MRI findings in PCNSL remains unclear. In contrast, recent images obtained with nuclear imaging and MRS showed characteristics similar to those of earlier images.

Because PCNSL is thought to show typical findings on neuroimaging, diagnosis is usually not difficult. However, because symptoms of PCNSL frequently worsen, neuroradiological surveys become insufficient for diagnosis, and neuroimaging results become atypical as a result of necessary treatments. Neuroimaging results in immunodeficient patients, including those with AIDS, are also atypical. As the present study has

shown, conventional neuroimaging before treatment increasingly yields atypical findings. We should be aware that various types of neuroimaging findings are possible. When PCNSL is suspected on the basis of symptoms, but neuroimaging findings are not typical, performing other diagnostic studies, including advanced neuroimaging and biopsy, is important<sup>11</sup>.

### Conclusion

Neuroimaging findings suggest that PCNSL is a disease affecting the entire brain. Some imaging findings are characteristic, but the frequency of atypical findings on conventional neuroimaging is increasing. Atypical neuroimaging results do not rule out PCNSL, even in immunocompetent patients.

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