More and less frequent imaging findings in progressive multifocal leukoencephalopathy (PML) with differentials

Poster No.: C-0033
Congress: ECR 2013
Type: Educational Exhibit
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Keywords: Head and neck, MR, Diagnostic procedure, Infection
DOI: 10.1594/ecr2013/C-0033

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Learning objectives

1. To describe common and less common manifestation forms of progressive multifocal leukoencephalopathy (PML)

2. To address differential diagnoses

3. To highlight the role of imaging modalities in the diagnosis of PML
PML is a fatal demyelinating disease of the central nervous system caused by JC virus (JCV). The pathogenesis of JCV infection is still incompletely understood. After primary infection usually occurring during childhood JCV persists in renal tubular epithelial cells. PML is believed to be the result of JCV reactivation during immunosuppression. PML is encountered in immunocompromised patients with hematological diseases undergoing chemotherapy, autoimmune disorders (e.g. systemic lupus erythematoses, Wegener’s granulomatosis, dermatomyositis, multiple sclerosis, etc.) or patients with liver or renal impairment, due to secondary reduction in CD4 T-lymphocyte count. In the last three decades, PML has emerged as a major complication of HIV-infection. Currently HIV infection accounts for 85% of all cases of PML and 5% of AIDS patients develop the disease. The prognosis of PML remains poor. The clinical presentation of PML is extremely varied, with neurological and psychiatric symptoms dependent on the location primarily affected including sensorial, motoric and behavioural alterations developing over weeks. Diagnosis of PML includes "histology" confirmed (JCV antigens detected by immunochemistry on cerebral biopsy), "laboratory" confirmed PML (JCV DNA detected by PCR in CSF) and "possible" PML when clinically/radiologically typical. The diagnostic hallmark of PML is the presence of multiple, usually well-demarcated demyelinating lesions and oligodendrocytes with enlarged nuclei containing intranuclear amphiphilic inclusions (1a-d). Reactive astrogliosis frequently shows giant bizarre astrocytes with atypical nuclei.
Common manifestation forms of PML

**CT:** On CT, unifocal or multifocal slightly hypodense areas in the subcortical and periventricular white matter, that coalesce at time, generally exhibiting no mass effect and no enhancement are expected in the early stages. With time, white matter abnormalities become more evident even on CT (2-3). **MRI:** On MRI, lesions are usually hypointense on T1 and hyperintense on T2-weighted imaging compared to normal white matter. Signal intensity as well as CT-attenuation changes are subject to temporal changes. The subcortical arcuate (U) fibers are typically involved at first, creating sharp, scalloped margins (Fig. 4-8). Rarely, faint contrast enhancement at the margins of the lesion may be encountered, particularly in the acute phase of demyelination. In HIV-patients receiving antiretroviral therapy (HAART), marked enhancement can be observed, particularly during the immune reconstitution syndrome. Most frequent sites involved by PML are the parietal, occipital and frontal lobes (Fig. 4). Infiltration of the corpus callosum commonly accompanies lobar involvement, but can rarely occur also solitary in its different parts mimicking lymphoma or high-grade astrocytoma at first presentation (Fig. 5-7). In these cases, the lack of enhancement and of restricted water diffusivity helps for further differentiation. **DD:** With time, lobar infiltration can become strikingly symmetrical involving either the frontal or parietal lobes (Fig. 8-9), or both as well as the periventricular white matter, generating features similarly to those present in toxic leukoencephalopathy (e.g. methotrexate, L-asparaginase, cytosine arabinoside, fludarabine and other chemotherapeutics, eventually potentiated by concomitant irradiation), HIV-encephalitis (spares the U-fibers and the contrast to white matter is more discrete) or microangiopathic encephalopathy. Less common manifestation forms of PMLPontomesencephalic localization of PML has been reported, but is rare. Sometimes, the long tracts (e.g. pyramidal tract) present with signal abnormalities secondary to transaxonal Wallerian degeneration caused by central involvement of the corona radiata. Basal ganglia lesions in PML are less common and are mostly accompanying lobar manifestations (Fig. 9-10). If isolated, however, ischemic, inflammatory or metabolic differentials should be considered. Solitary nodular lesions in the cerebral white matter are rare and generally represent early stages of disease (Fig. 13-15). Imaging characteristics depend mainly on their age. Active demyelination results in heterogeneous signal intensity often presenting with concentric target configuration. The peripheral halo represents active demyelination and inflammation whereas the core of the lesion reflects gliosis and presumably even necrosis. Differentiation from other tumefactive demyelinating diseases like multiple sclerosis (MS), or acute disseminated encephalomyelitis (ADEM) might be challenging. Posttransplant lymphoma (e.g. EBV-induced) may resemble PML on T1 and T2-weighted images, but its marked enhancement and marked restricted water diffusion help for differentiation. In later disease stages, these lesions shrink similarly to their MS counterparts and become better delineated. Multifocal, target-configured, large nodular white matter lesions may mimic ADEM or other demyelinating infectious complications like EBV-induced encephalitis, or infections such as toxoplasmosis.
Even early stages of brain abscess should be considered for differential as encapsulation and mass effect can entirely be absent, depending on the immune status. In the latter, the course of disease is however, more rapid. **Cortical involvement** is atypical and should primarily suggest other diagnoses. Nonetheless, sometimes even cortical gray matter may be involved mimicking other forms of **meningoencephalitis**, **ischemia** or **PRES**. Water diffusivity in PML is generally not restricted which is helpful for differentiation from **acute encephalitis** (e.g. herpes virus simplex-HSV-1, HHV- 6, or varicella-zoster virus) or **ischemia** (secondary to tumor-related hypercoagulation). However, depending on the degree of active demyelination and accompanying inflammation, restricted water diffusivity can be present temporarily at the margins of focal PML, surrounding a lesion core that exhibits high signal intensity on apparent diffusion coefficient (ADC) map images (Fig. 16-19). Thus, the target configuration of focal nodular PML lesions, reflecting different stages of virus related demyelination, is often displayed also by diffusion-weighted imaging (DWI). Restricted diffusion has been identified as characteristic in phases of rapid disease progression.
**Fig. 1:** The diagnostic hallmark of PML is the presence of multiple, usually well-demarcated demyelinating lesions and oligodendrocytes with enlarged nuclei containing intranuclear amphiphilic inclusions (1a-d). Reactive astrogliosis frequently shows giant bizarre astrocytes with atypical nuclei.

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Fig. 2: On CT, unifocal or multifocal slightly hypodense areas in the subcortical and periventricular white matter, that coalesce at time, generally exhibiting no mass effect and no enhancement are expected in the early stages. With time, white matter abnormalities become more evident even on CT (2a-b).

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Fig. 4: On MRI, lesions are usually hypointense on T1 and hyperintense on T2-weighted imaging compared to normal white matter. Signal intensity as well as CT-attenuation changes are subject to temporal changes. The subcortical arcuate (U) fibers are typically involved at first, creating sharp, scalloped margins (Fig. 4-5). Rarely, faint contrast enhancement at the margins of the lesion may be encountered, particularly in the acute phase of demyelination. In HIV-patients receiving antiretroviral therapy (HAART), marked enhancement can be observed, particularly during the immune reconstitution syndrome.

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Fig. 6: Infiltration of the corpus callosum commonly accompanies lobar involvement, but can rarely occur also solitary in its different parts mimicking lymphoma or high-grade astrocytoma at first presentation (Fig. 6). In these cases, the lack of enhancement and of restricted water diffusivity helps for further differentiation.

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Fig. 7: The lack of enhancement and of restricted water diffusivity helps for further differentiation from lymphoma.

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Fig. 8: With time, lobar infiltration can become strikingly symmetrical involving either the frontal or parietal lobes, or both as well as the periventricular white matter, generating features similarly to those present in toxic leukoencephalopathy (e.g. methotrexate, L-asparaginase, cytosine arabinoside, fludarabine and other chemotherapeutics, eventually potentiated by concomitant irradiation), HIV-encephalitis (spares the U-fibers and the contrast to white matter is more discrete) or microangiopathic encephalopathy.

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Fig. 10: Cerebellar PML manifestation (FLAIR image).

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Fig. 11: Cerebellar PML manifestation (FLAIR image).

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**Fig. 12:** Basal ganglia lesions in PML are less common and are mostly accompanying lobar manifestations (Fig. 12). If isolated, however, ischemic, inflammatory or metabolic differentials should be considered.

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Fig. 14: Solitary nodular lesions in the cerebral white matter are rare and generally represent early stages of disease (Fig. 14-15). Imaging characteristics depend mainly on their age. Active demyelination results in heterogeneous signal intensity often presenting with concentric target configuration. The peripheral halo represents active demyelination and inflammation whereas the core of the lesion reflects gliosis and presumably even necrosis.

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**Fig. 17:** Depending on the degree of active demyelination and accompanying inflammation, restricted water diffusivity can be present temporarily at the margins of focal PML, surrounding a lesion core that exhibits high signal intensity on apparent diffusion coefficient (ADC) map images (Fig. 17-18).

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Fig. 18: Depending on the degree of active demyelination and accompanying inflammation, restricted water diffusivity can be present temporarily at the margins of focal PML, surrounding a lesion core that exhibits high signal intensity on apparent diffusion coefficient (ADC) map images (Fig. 18).

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Conclusion

PML manifests with a broad spectrum of imaging features. Besides knowledge of preferential location, extent, temporal course, enhancement, results of functional imaging and clinical setting, recognition of imaging findings reflecting active demyelination may help the clinician in appropriately narrowing down the differential diagnosis.
References

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