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Immunotherapy is a promising treatment option for non–small-cell lung cancer patients. Immunotherapy clinical trials include for example PD-(L)1 and CTLA4 blockers, but also activating interleukins (IL). The related adverse events are different from that of chemotherapy-based treatment and new lesions can be the result of so called pseudo-progression instead of real tumor progression.[1,2] Differentiation among progressive disease, pseudo-progression, and infectious disease can be challenging, as was the case for the patient described below.

This patient was diagnosed with metastasized non–small-cell lung cancer (adenocarcinoma). At diagnosis, magnetic resonance imaging (MRI) of the brain was normal. First-line treatment consisted of four cycles of chemotherapy (gemcitabin/cisplatin) resulting in a partial response. As a maintenance treatment, she was treated with the immuncytokine Selectikine (modified IL-2 [NHS-IL2]) in a phase I trial (NCT00879866).[3] After 2 months, she presented with nausea, vomiting, and an altered mental status. Brain MRI showed extensive supra- and infratentoral perivascular enhancement, with additional leptomeningeal enhancement at the brainstem and pineal gland (Fig. 1). Extracranially, new liver metastases were found. Differential diagnosis of the brain lesions consisted of brain metastases, an (opportunistic) infection or polyoma JC virus causing progressive multifocal leukoencephalopathy (PML) as part of an immune reconstitution syndrome (IRIS) due to the immunotherapy, and pseudoprogression. Serum viral serology and cerebrospinal fluid cultures for polyoma JC, HIV, toxoplasma, CMV, HSC, VZV, mycobacteria, cryptococcus, and yeasts were negative. Cerebrospinal fluid cytology showed malignant cells. After 3 weeks she died; brain obduction showed extensive adenocarcinoma metastases (Fig. 2). Additional staining did not show an intracranial immune response (no influx of B-cells, T-cells, or macrophages).

In this patient, MRI findings were not equivocal. Brain metastases are located mostly at the border of gray and white matter and extensive perivascular enhancement is not a typical finding for brain metastases although some cases are described.[4,5] Brain MRI findings in PML-IRIS are consistent with the findings in our patient. Typical PML lesions

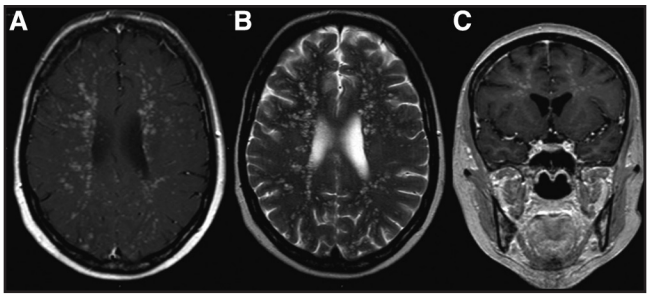

FIGURE 1. Brain MRI. Transverse T2-weighted images (*A*) and transverse (*B*) and coronal (*C*) contrast enhanced T1-weighted images show numerous punctiform hyperintense lesions at T2-weighted imaging, with enhancement after administration of gadolinium. The lesions follow a more or less curved pattern, consistent with perivascular distribution, without lesions at the gray-white matter interface.

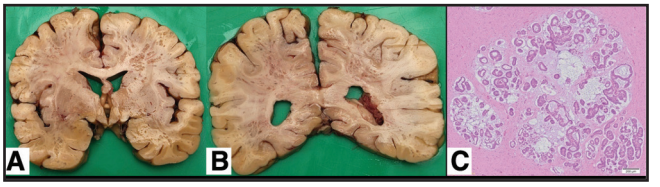

FIGURE 2. Brain autopsy. *A* and *B,* Macroscopic aspect of brain tissue show multiple millimetric nodules located along the perivascular spaces; (*C*) microscopy shows moderately differentiated tubuli with mucin-forming cilindric cells, consistent with adenocarcinoma metastases.

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are diffuse, with variable size and shape, mainly subcortical located and hyperintensive in T2-weighted images. They are found almost exclusively in the white matter with sparing of the periventricular white matter.[6] Contrast enhancement can be seen in PML-IRIS due to local inflammation and breakdown of the blood–brain barrier.[6] PML-IRIS has been increasingly diagnosed in patients treated with immunomodulation when T-cell function is restored after removal of immunosuppression.[7]

In conclusion, miliary brain metastases are rare and remain a diagnostic challenge especially in the era of immunomodulation.

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