

**CASE REPORT**

# Can pulmonary sarcoidosis trigger a progressive multifocal leukoencephalopathy? Considerations from a case series and a review of literature

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**Key Clinical Message**

Progressive multifocal leukoencephalopathy (PML) is a severe infectious brain disease with lethal outcome mainly seen in immunocompromised subjects. Herein, we describe a new form of PML with different outcome which was observed in patients suffering from systemic sarcoidosis. Thus, we raise the question whether preexisting sarcoidosis might predispose for or even trigger PML.

**KEYWORDS**

immunology, opportunistic infection, progressive multifocal leukoencephalopathy, sarcoidosis

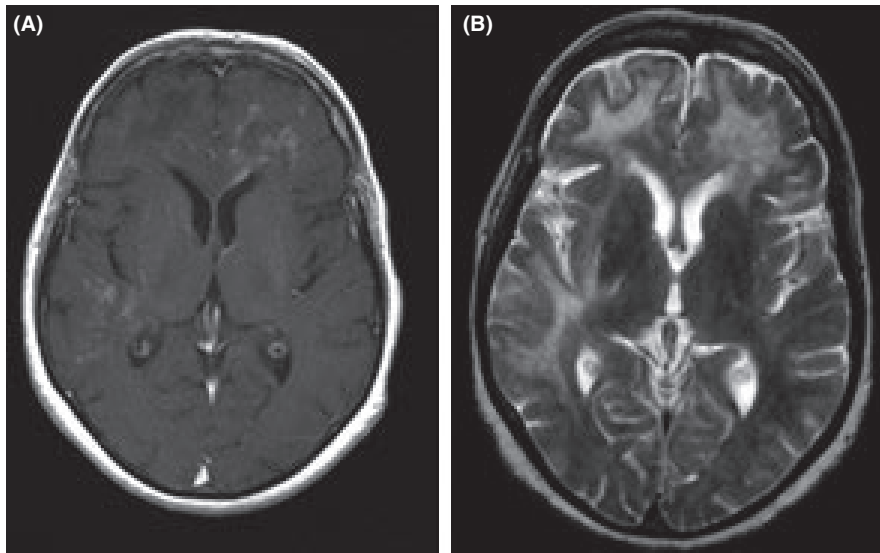
## 1 | BACKGROUND

Progressive multifocal leukoencephalopathy (PML) constitutes a severe demyelinating disease of the brain, caused by the infection of JC virus (JCV).<sup>1</sup> It is usually refractory to treatment and mortality is high. PML commonly occurs in immunocompromised subjects and has recently received increased attention due to its association with antibody therapies in multiple sclerosis.<sup>2,3</sup> Asymptomatic primary infection with JC virus is assumed to occur in childhood or youth; serum antibodies can be found in up to 85% of adults.<sup>4</sup> However, a coincidence of PML and sarcoidosis has rarely been described, thus posing a particular diagnostic challenge. Here, we present PML which manifested spontaneously in three patients who also had a diagnosis of pulmonary sarcoidosis.

## 2 | CASE REPORTS

### 2.1 | Case 1

A 76-year-old female patient was admitted to hospital due to a rapid cognitive decline within 2 months. Relatives described a considerable change in personality with confusion and agitation. Neurological examination revealed cognitive impairment (MMSE 19/30) and a dysexecutive syndrome with poriomania, but no sensorimotor deficits. She had a medical history of COPD, untreated pulmonary sarcoidosis, and breast cancer 2 years before, treated by breast resection, axillary dissection, local radiation, and systemic hormone therapy. Pulmonary sarcoidosis had been diagnosed 2 years before on the basis of bronchoscopy with transbronchial



**FIGURE 1** (A and B) T1-weighted MRI and T2-weighted MRI show diffuse confluent bilateral hyperintense lesions in the white matter from the frontal to the temporal lobes—some of these lesions show enhancement as sign of blood-brain barrier leakage

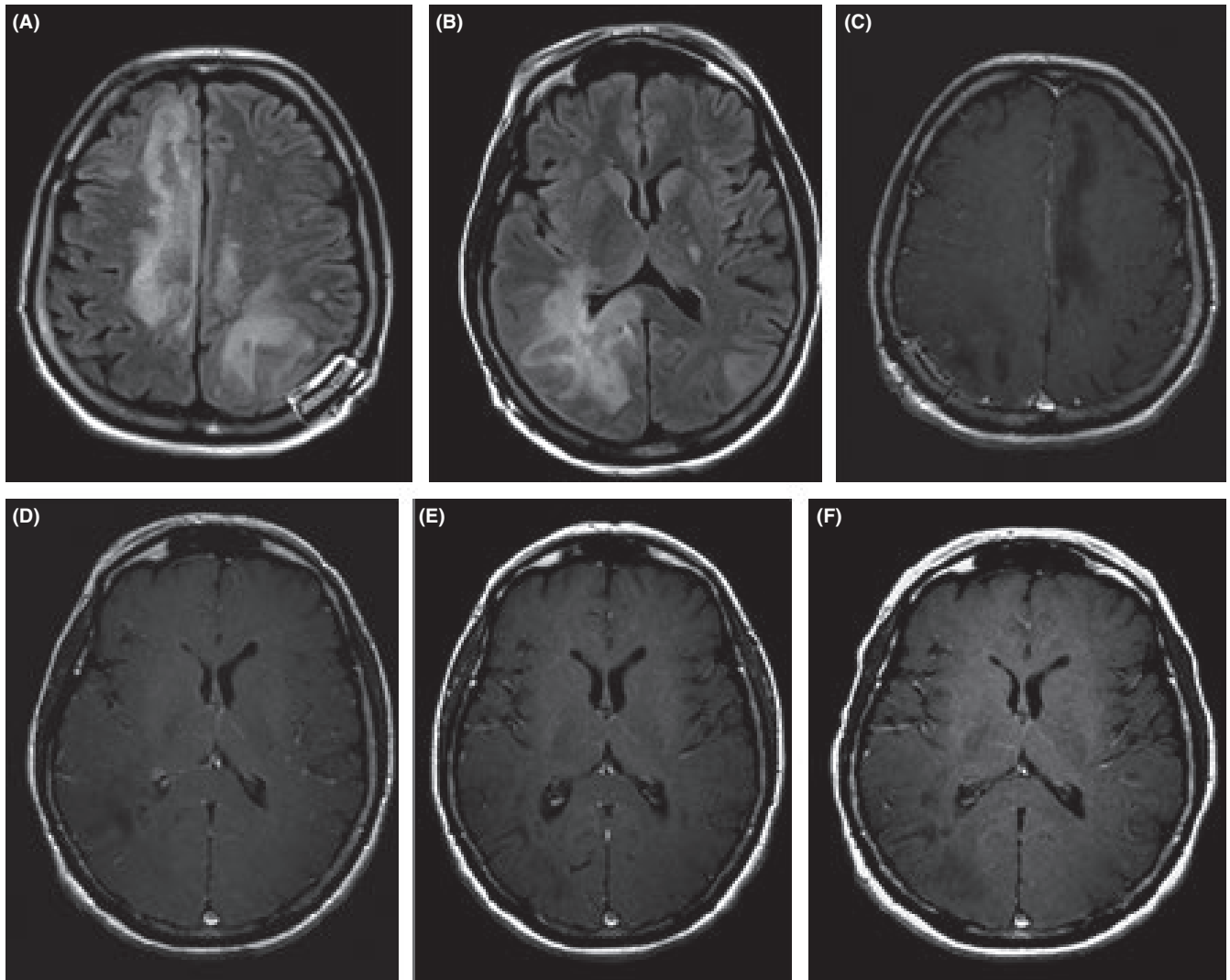
biopsy, where histologically non-necrotizing granuloma had been detected. Laboratory tests were unremarkable apart from absolute lymphopenia (0.68 G/L) with otherwise normal blood cell findings. HIV and syphilis infections were ruled out serologically. Chest X-ray detected two consolidations in the right upper lobe resembling granuloma. Cranial MRI showed diffuse confluent bilateral widespread hyperintense lesions in the white matter extending from the frontal to the temporal lobes with multifocal contrast enhancement at the edges of the lesions (Figure 1A,B).

Cerebrospinal fluid (CSF) revealed a mild lymphocytic pleocytosis (24/3 cells) with a single plasma cell, as well as a disrupted blood-brain barrier, an intrathecal immunoglobulin G production, and positive oligoclonal bands. Ultrasensitive PCR finally detected JC virus DNA (130 copies/mL) in CSF, establishing the diagnosis of PML. The presence of an intrathecal immune reaction, positive contrast enhancement, and the rapid clinical deterioration of cognitive function were interpreted as immune reconstitution inflammatory syndrome (IRIS) in an already longer standing but undetected cerebral PML. Therefore, a pulse of high dose prednisolone i.v. was administered for 7 days. In addition, mirtazapine 30 mg per day was given orally. Within 4 weeks, stabilization of behavior and cognition was observed and the patient was dismissed to her family. Two years after the diagnosis, the patient is alive at home in a stable cognitive condition with mild ataxia.

## 2.2 | Case 2

A 54-year-old woman presented complaining about fatigue, bilateral visual impairment, vertigo, and gait instability. Neurological examination revealed left-sided hemianopia, dysarthria, right-sided hemiparesis (MRC scale: upper limb 4/5, lower limb 2/5) accompanied by a positive Babinski sign, and gait ataxia. An attention deficit disorder and disturbance of memory were apparent. She had a medical history

of arterial hypertension, chronic hepatitis B, and pulmonary sarcoidosis. Sarcoidosis had been diagnosed six years before on the basis of mediastinal lymph node biopsy and chest imaging, consistent with stage II (bilateral hilar adenopathy and reticular opacities). An examination of bronchoalveolar lavage (BAL) fluid was done 3 years later and confirmed a slight lymphocytic alveolitis with a predominance of CD4+ T cells. Angiotensin-converting enzyme (ACE) levels at that time were normal. Pulmonary function tests were initially normal, but repeated investigations revealed pulmonary restriction, which led to initiation of a combined inhalative therapy of a corticosteroid and  $\beta_2$ -agonists. Immunosuppressive treatment was not started. Brain MRI at 3.0 Tesla at time of the actual admission showed diffuse areas of high signal intensity involving the white matter of the left frontal, right parietal, and both occipital lobes on T2/FLAIR-weighted images (Figure 2A,B). There was no mass effect or contrast enhancement but the lesions appeared partially hypointense on T1-weighted scans (Figure 2C). At first, these findings were felt to be suggestive of vasculitis. Respective testing for autoantibodies (ANA, ENA, ANCA, and cardiolipin-antibodies) was done, but yielded unremarkable findings. CSF analysis showed a normal cell count and normal concentrations of total protein, glucose, and lactate, but elevated albumin and immunoglobulin G levels. Oligoclonal bands were absent. Extensive antibody testing provided no evidence for Lyme's disease or viral infections (herpes simplex, tick-borne encephalitis, varicella zoster, Epstein-Barr virus, adenovirus, and coxsackie virus) in CSF and serum examinations. Routine blood count and chemistry were repeatedly normal. Testing for HIV was negative. The ACE level was increased (86.9 U/L; normal range: 18-55). Computed tomography (CT) of the thorax showed atelectasis of both upper lobes of the lungs and fibrosis, with distortion of the architecture and nodular lesions in both lungs, along with hilar and mediastinal lymphadenopathy considered typical for sarcoidosis.



**FIGURE 2** (A and B) T2/FLAIR-weighted 3.0 Tesla MRI shows diffuse areas of high signal intensity involving the white matter of the left frontal, right parietal, and both occipital lobes. (C) No mass effect or contrast enhancement on T1-weighted MRI but the lesions appear partially hypointense. (D) T1-weighted scan shows slight contrast enhancement—suggestive of mild IRIS. (E) Postcontrast T1-weighted scan shows reduction of size of lesions. (F) Postcontrast T1-weighted scan reveals no changes up to 4 y after diagnosis

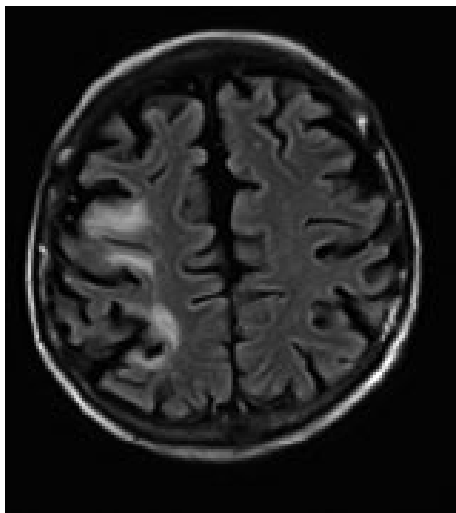
Whole-body positron emission tomography (FDG-PET) examination was reported to be consistent with a vasculitis due to a putatively increased tracer uptake of large vessels. In the absence of clear-cut results, it was decided to obtain a stereotactic brain biopsy of the right occipital lesion. Histology revealed (peri)vascular inflammation, but showed no evidence for granulomas or polynuclear giant cells which would have been indicative of neurosarcoidosis. Integrating all these findings, the working hypothesis of a systemic vasculitis was established. Oral prednisolone treatment (1 mg/kg) combined with cyclophosphamide (100 mg/d) and prophylactic antiviral protection using tenofovir because of chronic hepatitis B was initiated 3 weeks after admission. The patient continued to deteriorate markedly 1 week after applying cyclophosphamide, paralleled by a progression in size, and confluence of lesions on brain MRI. The imaging characteristics

and the lesion evolution finally led to considering the differential diagnosis of PML. JCV testing was performed and yielded 4.6 million copies in urine and 150 copies/mL in the CSF. An immunohistochemical reaction with the SV40/JC antibody was also seen in the brain tissue specimen. Upon re-examination, cyclophosphamide and prednisolone were discontinued. A therapy with mefloquine 250 mg for consecutive 3 days followed by once weekly doses and 15 mg mirtazapine once daily was initiated. One week after cessation of immunosuppression, slight contrast enhancement was seen on MRI suggestive of a mild IRIS (Figure 2D). The patient subsequently continued to improve clinically, paralleled by a reduction of the size of cerebral MRI lesions (Figure 2E). At that time, repeated testing only showed a slightly positive reaction for JCV in blood samples and JCV copies in urine fell substantially to 29 440 copies/mL, while JCV could not

be detected in CSF anymore. Follow-up outpatient visits to our department were done regularly for up to now 4 years. Recently, she has ceased taking the medication comprising mefloquine and has further improved clinically. At her last visit, no visual impairments nor residual hemianopia or aphasia were noted. Motor function of the lower limb had returned to normal, and strength of the right upper limb had remarkably improved to 4+/5 on the MRC scale. Gait ataxia had improved and walking with a cane was possible. There were no changes on repeated MRI of the brain (Figure 2F).

### 2.3 | Case 3

A 63-year-old female patient was admitted to the hospital due to a recent left-sided hemiparesis and hypaesthesia of the left lower limb since 2 months. History taking revealed recurring fever the past few days before admission. Preexisting diseases included COPD with long-term oxygen therapy and recently diagnosed combined pulmonary fibrosis and emphysema. At the time of admission, the condition of the patient was considerable reduced due to stress dyspnoea. Neurological examination showed notably left-sided spastic ataxic hemiparesis. Cranial MRI revealed right frontoparietal band-shaped hyperintense lesions on T2/FLAIR-weighted images (Figure 3), mainly subcortically located including the U-fibers, raising the suspicion of PML. Contrast enhancement or mass effect was missing. A brain positron emission tomography examination (FDG-PET) detected hypometabolism of the right parietal, temporal and right frontal lobes, corresponding to the alterations seen on MRI. CSF showed a mild pleocytosis (12/3 cells), a highly positive JCV antibody Index (3.49) and positive oligoclonal bands with otherwise normal cell findings. In addition, ultrasensitive PCR revealed JC virus DNA in CSF below the detection limit. PCRs of



**FIGURE 3** T2/FLAIR-weighted images reveal right frontoparietal band-shaped hyperintense lesions mainly subcortically located, including the U-fibers

HSV, VZV, and CMV were negative. Laboratory tests repeatedly revealed mild leukopenia, decreased B cells, and T-helper cells as well as an increased JCV antibody level (234 AU/ $\mu$ L).

Angiotensin-converting enzyme (ACE) level was increased (124.1 U/L; normal range: 18–55), whereas HIV infection was ruled out in serum. Chest X-ray detected pulmonary fibrosis and emphysema. Computed tomography (CT) of the thorax and abdomen yielded an interstitial lung disease as well as hepato- and splenomegaly. Additionally, a bone marrow biopsy showed multiple epithelioid cell granuloma—compatible with a previously undiagnosed sarcoidosis. Due to global respiratory insufficiency in the course of pneumonia, the condition of the patient worsened. She thus was transferred to ICU, where she passed away 4 weeks after admission. Postmortal brain biopsy of the cortical right parietal imaging alterations hardened the diagnosis of PML histologically by the findings of demyelination, bizarre astrocytes, and foam cells.

### 3 | DISCUSSION

Until now, only few cases on the coincidence of PML and sarcoidosis have been reported.<sup>5–8</sup> Our case series adds new important observations and thus helps raising the level of alertness to this rare brain infection in these conditions.

These three case reports from different departments demonstrate that diagnosing PML in apparently immunocompetent patients with a history of sarcoidosis is challenging. In these PML, patients an in-depth medical history and differential diagnosis revealed sarcoidosis without systemic treatment as single cause of a potential immunocompromised state. Our patients suffered primarily from minimal or occult immunosuppression in sarcoidosis several years before the manifestation of the opportunistic cerebral infection. Thus, PML can follow or perhaps even been triggered by a pulmonary sarcoidosis and show diverse clinical outcomes: there was one favorable and one moderate outcome, but also one death. This prompted us to pool these rare observations from three departments, to raise suspicion of PML in such a scenario.

The MRI features of PML with hyperintense lesions on T2-weighted and FLAIR sequences which are asymmetric involve the U-fibers and relatively spare periventricular white matter are characteristic but not pathognomonic. An involvement of gray matter structures such as basal ganglia or thalamus can be seen.<sup>9</sup> There is one case report with similar clinical and MRI features like in our first patient.<sup>10</sup> This patient also suffered from idiopathic lymphopenia as unique reason for immunosuppression, but he had no diagnosis of pulmonary sarcoidosis. PML was detected by brain biopsy, he was put on mirtazapine 30 mg/d and also remained in a stable condition for 1 year of follow-up.

Current hypotheses on the pathogenesis of sarcoidosis assume that this multisystem granulomatous disorder is induced by a non-degradable antigen-inducing immune reactions, which are mediated by a panel of immune cells of the innate and adaptive immune system.<sup>11</sup> These immune reactions lead to an accumulation of immune cells (alveolar macrophages, T cells, and neutrophils), resulting in granuloma formation and remodeling of the lung and other affected tissues.<sup>11</sup> Since the pathogenesis of sarcoidosis has not entirely been clarified so far, we can only assume that sarcoidosis triggers the development of opportunistic brain infections and that genetic predisposition, amongst others, plays a role when the question is raised whether not every sarcoidosis patient develops PML. However, our observations cannot prove causation between these two conditions, yet point to the fact of co-occurrence which should raise alertness of clinicians to consider this possibility.

## 4 | CONCLUSION

Our cases highlight the necessity to pertain carefully with respect to potential differential diagnoses in the context of patients with a history of pulmonary sarcoidosis and recent neurologic or neuropsychological symptoms and unclear imaging findings—even in the absence of immunosuppressant therapy—and emphasize that PML needs to be considered. These case series should thus raise alertness toward this coincidence and prompt further reports in the literature. The variety of clinical outcomes raises another fundamental hitherto unanswered question: Could preexisting pulmonary sarcoidosis itself be considered as a triggering factor for PML or are these conditions coincidental findings?

## CONFLICT OF INTEREST

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in subject matter or materials discussed in this manuscript.

## AUTHOR CONTRIBUTION

IG: collected and prepared data and wrote the paper. EF: conceived the presented idea, collected and prepared data, supervised the progress of the manuscript at all stages, and critically revised the final version of the manuscript. CE: conceived the presented idea, gathered and prepared data, supervised the

progress of the manuscript at all stages, and critically revised the final version of the manuscript. MF: collected and prepared data and critically revised the final version of the manuscript. AP: collected and prepared data. TS: collected and prepared data and critically revised the final version of the manuscript.

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