doi:10.1111/j.1750-3639.2009.00362.x

A 76-YEAR-OLD WOMAN WITH PARAPLEGIA

Jan Rémi, Thomas Pfefferkorn, Fatima B. König, Hans Lassmann, Wolfgang Brück, Markus Holtmannspötter, Andreas Straube, Hans A. Kretzschmar and Ulrich Schüller

From the Departments of Neurology (J.R., T.P., A.S.), Neuroradiology (M.H.), Neuropathology (H.A.K., U.S.) of the University of Munich, Germany, the Department of Neuropathology of the University Medical Center of Göttingen, Germany (F.B.K., W.B.), and the Center for Brain Research of the University of Vienna, Austria (H.L.).

CLINICAL HISTORY AND NEUROIMAGING

A 76 year old woman was admitted to a spinal trauma hospital after a collapse at home with paraplegia and total loss of deep tendon reflexes of unknown duration. Upon admission she was responsive but not well orientated. A spinal MRI showed T2 signal enhancement from Th4 to L2, without revealing evidence of the etiology. Over the course of the next 3 days her mental status decreased to where she could only be woken up with strong pain stimuli. Leukocytosis (30.3 G/l) and fever (39°C) were noted. In a cerebral computed tomography, several hypodense white matter lesions were visible. The cerebrospinal fluid (CSF) contained 61 cells/µl with 3.33 g/l protein and 1.8 mmol/l glucose (serum: 6.0 mmol/l) and treatment with broad spectrum antibiotics and glucocorticosteroids was started.

On hospital day 5 she was transferred to our neurological intensive care unit because of deteriorating mental status and the need for mechanical ventilation. On day 12, an axial FLAIR-weighted MRI showed large confluent white matter lesions in the brain (Figure 1). Similar abnormalities were found in the spinal cord. The lesions showed no signal enhancement on diffusion weighted imaging, but had patchy gadolinium contrast enhancement. CSF cell, protein and glucose levels remained stable over several lumbar punctures, and CSF specific antibody production was shown with CSF specific oligoclonal bands. Microbiological CSF analyses were negative for bacterial or viral pathogens, including JC-virus and enteroviruses. Anti-aquaporin 4 antibodies were not detectable. The peripheral leukocytosis of her blast crisis peaked at 102 G/l. No BCR-ABL rearrangement was detectable. The patient's condition continued to deteriorate despite anti-microbial and steroid treatment. The patient died on hospital day 16.

Over the three and a half years prior to admission, the patient had unintentionally lost 10–15 kg of body weight, and there had been an extensive work-up for a neoplasm which yielded no specific pathological results. A bone-marrow biopsy three years ago had not retrieved enough bone marrow cells at that time to be conclusive, the blood leukocyte levels in the previous three years were around, the high normal limit (but never above). Her other past medical history was non-contributory.

PATHOLOGY

The post mortem analysis secured the diagnosis of an acute myeloid leukemia (AML, sub-type M2) in bone marrow, spleen (weight: 380 g) and liver. No other neoplasm was found. The analysis of brain tissue revealed large, partly confluent lesions in the white matter of both cerebral hemispheres as well as the spinal cord. A representative gross image is shown in Figure 2 demonstrating a well-demarcated lesion in the right occipital lobe. Distinct lesional areas within the cerebral white matter are visible in a Luxol-Fast-Blue stain (Figure 3). Axonal destruction varied, but was severe in some areas. GFAP+ reactive astrocytes and macrophages with LFB-positive material (Figure 3, insert) were detectable throughout the lesions. C9neo+ complement deposits were also present at some sites (Figure 4, brown signal). Blood vessels as well as perivascular spaces within the lesions were packed with myeloblasts (Figure 5). The spread of myeloblasts was most severe within the lesions, but they could also be found throughout the whole brain parenchyma outside the lesions.

What is the diagnosis?

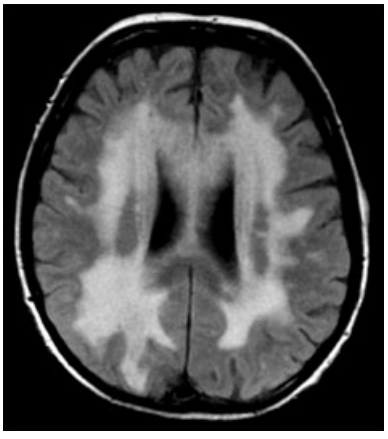

Figure 1.

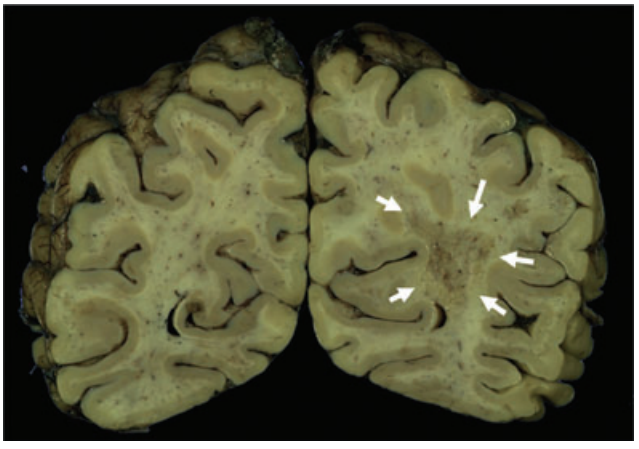

Figure 2.

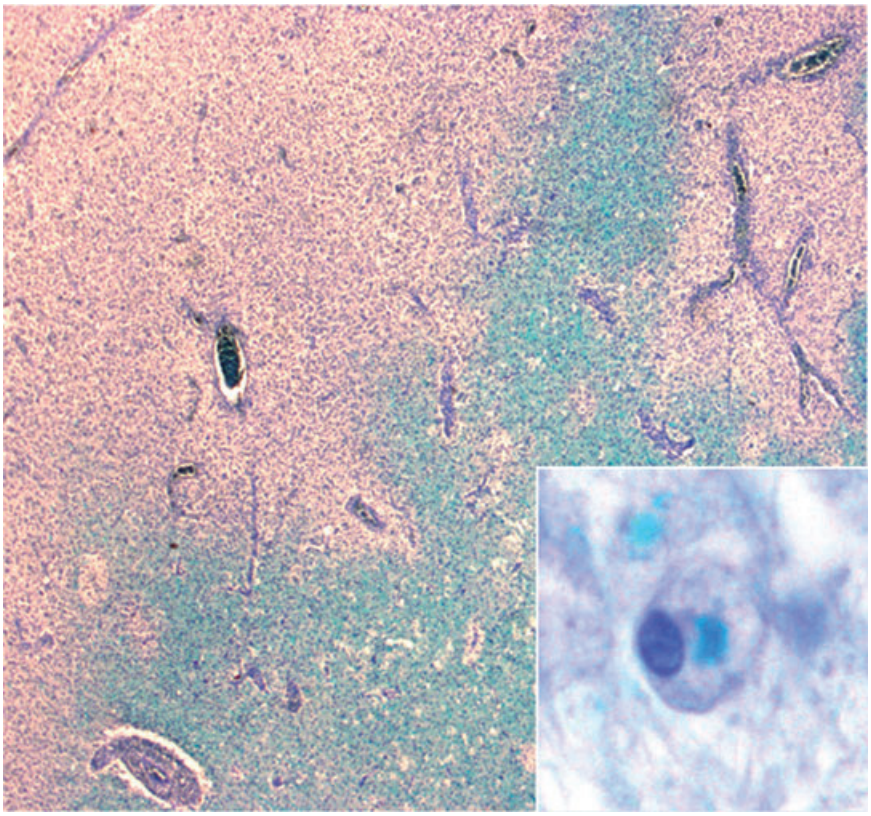

Figure 3.

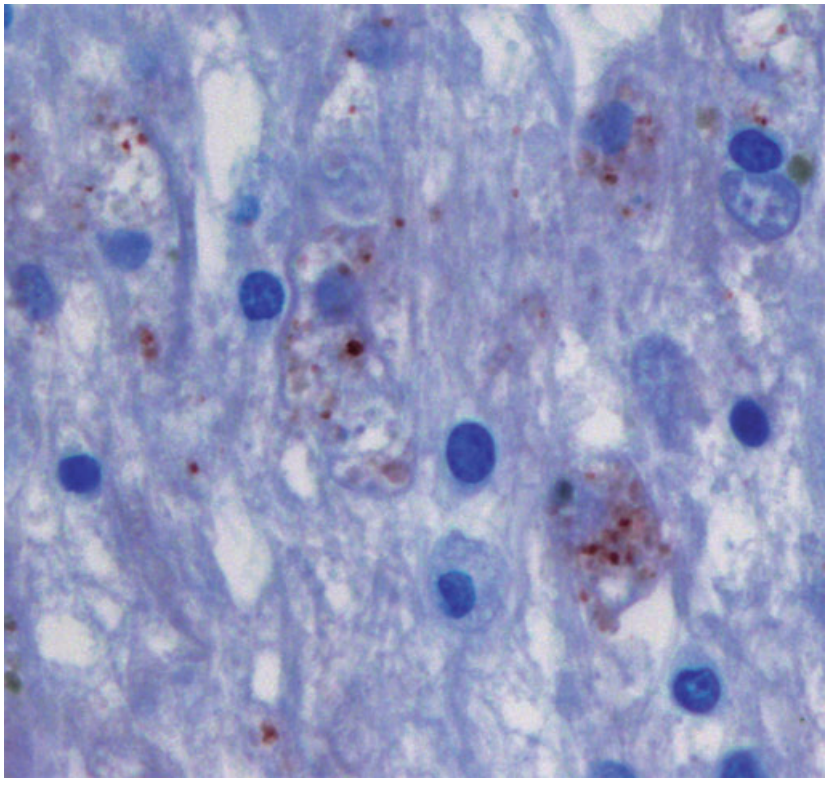

Figure 4.

Brain Pathology **20** (2010) 507–510

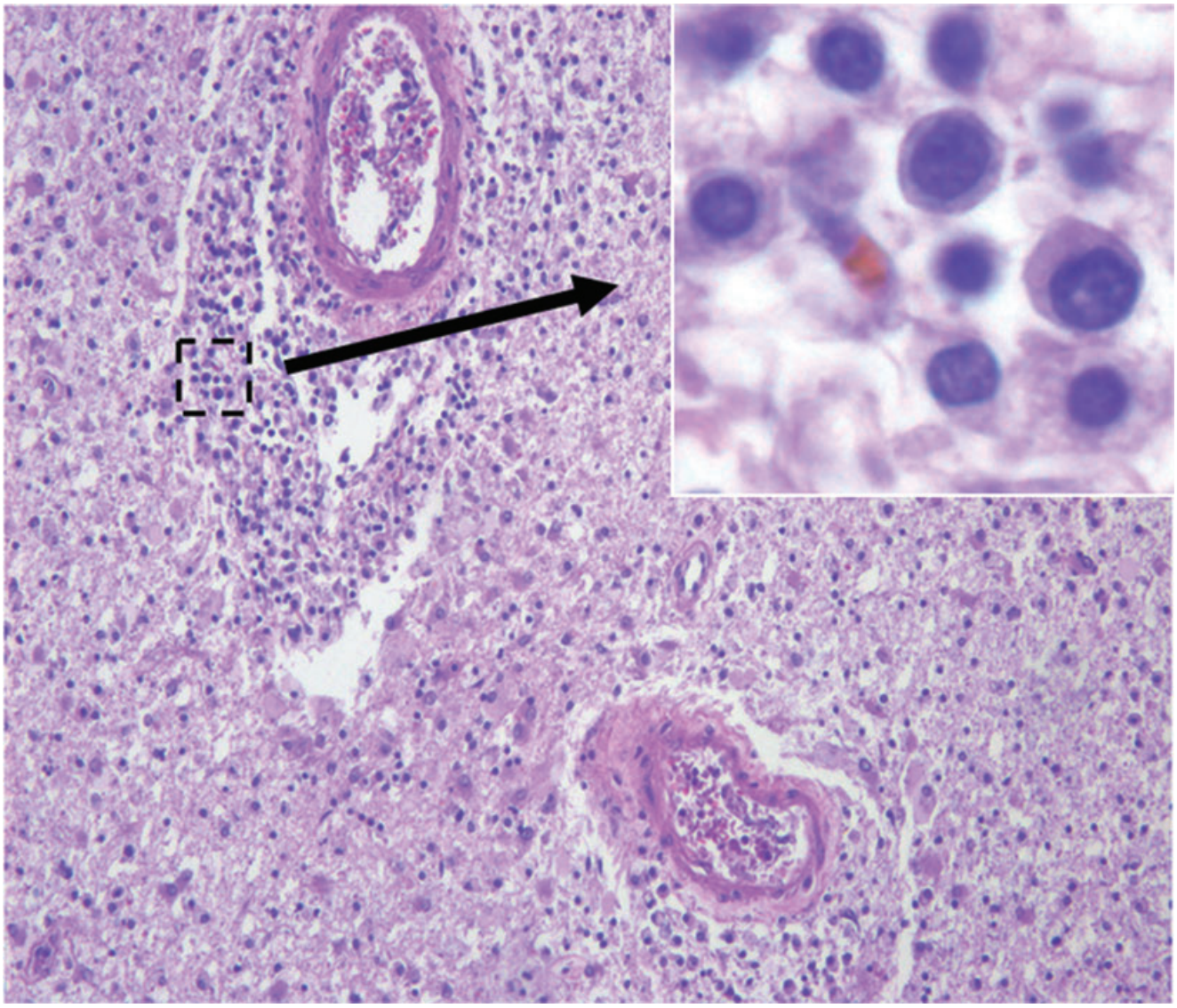

Figure 5.

DIAGNOSIS

CNS spread of untreated acute myeloid leukemia associated with acute demyelination

DISCUSSION

C9neo+ complement deposits were also present at sites of active demyelination (Figure 4, brown signal). This is a pattern of pathology that is typically seen in the antibody- and complement-mediated pattern II of multiple sclerosis lesions according to the classification scheme of Lucchinetti *et al* (4).

Patients suffering from leukemias may develop CNS complications of their disease. Spread of the disease into the central nervous system (CNS) is a rare example, which is generally less frequent in adults than in children (2, 8), and particularly uncommon in untreated patients, where only single cases are reported (5). Leukoencephalopathy is more common and potentially life-threatening. It may have several different etiologies, for example demyelination as a paraneoplastic disorder (1), progressive multifocal leukoencephalopathy after a JC-virus infection (3) or multifocal necrotizing leukoencephalopathy after chemotherapy (6). However, as these examples illustrate, reports on leukoencephalopathy in relation to leukemia may be ambiguous because the patients typically receive treatment with potential neurotoxicity.

Recently, a CNS relapse of an AML associated with leukoencephalopathy was suggested in an adult patient that had only been treated with cytarabine, which is not thought to penetrate the CNS, making a neurotoxic effect unlikely (7). MRI in that patient showed widespread leukoencephalopathy, but there was only indirect evidence for a role of a parenchymal CNS spread of the AML. Myeloblasts were found in the CSF and the leukoencephalopathy improved after chemotherapy, but no brain tissue was examined. That patient could be discharged without any neurological symptoms.

Our patient had very similar pathological features on MRI, but she had not been treated with any chemotherapeutic agents at all. In her case, though, the CNS-spread of the AML and the histopathologic pattern of the severe and extensive leukoencephalopathy could be shown in post mortem analysis. Our patient was seriously affected by a CNS-spread of the AML which may have been present for years, as suggested from her past medical history, and finally resulted in the patient's death from a blast crisis. Autopsy revealed active demyelination with complement deposits that extended over the cerebrum and myelon (spinal cord). While pronounced axonal destruction and complement-mediated demyelination can be typical for neuromyelitis optica (NMO), the patient had no clinical signs of NMO and we failed to detect any aquaporin-4 antibodies, arguing against this possibility.

In summary, we present a patient with CNS spread of an untreated acute myeloid leukemia, which is a very uncommon finding. Moreover, it was associated with acute demyelination and axonal destruction. We suggest that such demyelination may occur after and be related to the CNS spread of myeloblastic leukemic cells. Whether immunosuppression itself may trigger acute demyelination or exacerbation of a chronic multiple sclerosis or whether further mechanisms of immune system modulation related to AML are involved in the reported scenario need to be investigated in further studies and experimental settings. By all means, we believe that our case strengthens the need to strictly monitor CNS functions of AML patients.

REFERENCES

1. Jaster JH, Dohan FC Jr, O'Brien TF (2003) Demyelination in the brain as a paraneoplastic disorder: candidates include some cases of leukemia and non-Hodgkin's lymphoma. *Ann Hematol* **82**:714–5.
2. Johnston DL, Alonzo TA, Gerbing RB, Lange BJ, Woods WG (2005) Risk factors and therapy for isolated central nervous system relapse of pediatric acute myeloid leukemia. *J Clin Oncol* **23**:9172–8.
3. Kesari S, Akar S, Saad A, Drappatz J, Koralnik IJ, DeAngelo DJ (2008) Progressive multifocal leukoencephalopathy in a patient with relapsed acute myelogenous leukemia. *J Clin Oncol* **26**:3804–7.
4. Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H (2000) Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol* **47**:707–17.
5. Maynor ML (1989) Neurological manifestations as the initial presentation of acute myelogenous leukemia. *Am J Emerg Med* **7**:481–4.
6. Robb J, Chalmers L, Rojiani A, Chamberlain M (2006) Multifocal necrotizing leukoencephalopathy: An unusual complication of acute leukemia. *Arch Neurol* **63**:1028–9.
7. Schumann, M., Kiewe P, Hartlieb S, Neumann M, Schilling A, Koch HC *et al.* Diffuse Leukoencephalopathy and Brain Edema: Unusual Presentations of CNS Relapse of Acute Myeloid Leukemia. *J Neuroimaging*, (e-pub ahead of print) DOI: 10.1111/j.1552-6569.2008.00300.x.
8. Stewart DJ, Keating MJ, McCredie KB, Smith TL, Youness E, Murphy SG *et al* (1981) Natural history of central nervous system acute leukemia in adults. *Cancer* **47**:184–96.

ABSTRACT

A-76-year old woman was admitted to the hospital with paraplegia after a collapse at home. Magnetic resonance imaging showed white matter lesions from Th4 to L2 as well as large confluent white matter lesions in the cerebrum. Within 3 days, the patient's mental status decreased dramatically and she finally died on day 16 after her fall. Autopsy examination revealed an acute myeloid leukemia, which had not previously been diagnosed and which had never been treated. In the CNS, we found spread of myeloblasts in combination with acute demyelinating lesions which corresponded to the antibody- and complement-mediated pattern II of multiple sclerosis lesions. This case implies that association of acute myeloid leukemia and acute CNS demyelination needs to be discussed and suggests that AML patients need to be strictly monitored for CNS functions.