Freiburg Neuropathology Case Conference: a Diffusely Infiltrating Lesion

**Clinical Case**
A 44-year-old farmer presented with complex partial seizures and headache for 9 months. An initial magnetic resonance imaging (MRI) exam revealed an infiltrating lesion within the left frontotemporal region and the right temporal lobe (Figure 1). A stereotactic brain biopsy in September 2008 yielded unspecific findings with diffuse hypercellularity and reactive changes. Therefore, no therapy was initiated. The patient was readmitted in May 2009, after he had suffered a generalized seizure. Upon admission he was comatose with a fixed and dilated left pupil. Emergency intubation was performed, a ventricular drainage was placed, and steroids and osmotherapy were given because of increased intracranial pressure (ICP) and signs of uncal herniation. A second MRI was performed revealing an increase of the space-occupying effect as well as a new lesion within the left-sided inferior temporal gyrus (Figure 2). Gross total removal of the frontobasal and temporomesial portions of the lesion was achieved via a left pterional craniotomy. The temporo-dorsal lesion was approached via a second craniotomy and could be removed entirely. In spite of the removal of the space-occupying lesions, the patient had elevated ICP and a very slow recovery phase after anesthesia. A second ventricular drainage and ICP probe were placed. The clinical course was complicated by pneumogenic sepsis and the patient remained in a critical condition. When the histological diagnosis of a multifocal glioblastoma multiforme was made, intensive care therapies were not expanded and the patient died of circulatory arrest 4 days after emergency admission.

**Imaging**
The initial MRI exam of September 2008 demonstrated a diffusely infiltrating lesion involving the left frontal lobe as well as mesial parts of both temporal lobes. On fluid-attenuated inversion-recovery (FLAIR) images the lesion appeared hyperintense, showed some space-occupying effect, and a 37 mm × 20 mm × 42 mm-sized, nodular component was present within the left-sided frontal lobe (Figure 1). After administration of gadolinium (Gd) the lesion did not show any signs of blood-brain barrier disruption on T1-weighted images (not shown). The MRI exam after emergency admission of May 2009 revealed an increase of the space-occupying effect of the diffusely infiltrating lesions. An additional, initially not clearly identifiable lesion was finally depicted on FLAIR images as well as on diffusion-weighted images (DWI) within the left-sided inferior temporal gyrus. Still no disruption of the blood-brain barrier was identified on T1-weighted images after administration of Gd (Figure 2).

**Differential Diagnosis**
*Viral encephalitis*: increased signal on T2-weighted images, swelling of the cortex and the white matter are imaging findings, commonly present in encephalitis. Yet the initial clinical presentation, the absence of a blood-brain barrier disruption, as well as normal findings within the cerebrospinal fluid examination made us discard this potential differential diagnosis.

*Limbic encephalitis*: comparable imaging findings may be found in limbic encephalitis, although nodular components are rarely seen. The patient did not have any underlying tumor that would explain the limbic encephalitis, known to be a paraneoplastic syndrome.

**Figures 1a to 1c.** Initial brain MRI, September 2008. A hyperintense infiltrating lesion is seen in the left- and right-sided mesial temporal lobe (a, b, white arrows) as well as in the left-sided frontal lobe on FLAIR images (a–c, white arrowheads). A nodular portion can be delineated within the left-sided frontal lobe (a–c, black arrows), making the final diagnosis more difficult.
Progressive multifocal leukoencephalopathy: usually involves the periventricular white matter, rather than the cortex. It is often localized within the temporoparietal region. The patient was not immunocompromised making this diagnosis rather unlikely.

Lymphoma: lymphoma may appear as a diffusely infiltrating mass, yet contrast enhancement is present in most cases. Primary central nervous system (CNS) lymphomas often involve the corpus callosum, not touched in this patient. Yet an atypical, nonenhancing CNS lymphoma remains a potential diagnosis in our case.

Low-grade glioma: low-grade gliomas appear hyperintense on T2-weighted images and usually do not enhance on T1-weighted images after administration of Gd. They show diffuse infiltration of the white matter and may expand the adjacent cortex.

Cerebral gliomatosis: tumor involving at least two lobes of the brain. MR pattern is infiltrative with enlargement of cerebral structures. The nodular lesion has to be considered an atypical finding in gliomatosis cerebri. The dynamics of the infiltrative lesion with a benign initial histology and new focus appearing only 8 months later is compatible with the diagnosis. Contrast enhancement as well as a restricted diffusion on DWI may be observed in cases of local dedifferentiation.

Cerebral gliomatosis was considered the most likely diagnosis, viral encephalitis, limbic encephalitis, progressive multifocal leukoencephalopathy, lymphoma, and low-grade glioma seemed less probable.

**Histology**
The stereotactic brain biopsy in September 2008 (Figures 3a and 3b) showed CNS tissue with slightly increased cell number and diffuse microglia activation (Figure 3c). High proliferation activity could not be