OCTOBER 2004: A 49-YEAR-OLD MAN WITH PROGRESSIVE DEMENTIA

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Clinical history. A 49-year-old right-handed man developed progressive cognitive difficulties over a 4-month period. Recent memory was impaired. He was unable to do the payroll at his company and would get lost in familiar surroundings. There were word-finding and language difficulties. He had associated fatigue, anorexia, daytime somnolence and weight loss of 30 pounds. Gait imbalance and urinary incontinence developed later.

He had a past history of transfusion-associated Hepatitis C, chronic bronchitis, and anxiety. There was no history of chronic alcohol or drug abuse. There was no family history of early dementia.

On examination he was afebrile and normotensive. He was lethargic but would follow basic commands. His level of alertness waxed and waned during the course of his hospital stay. His language was mainly intact with mild dysarthria and dysnomia. Cranial nerve examination was normal. He had increased tone in both lower extremities. The left arm tone was increased with 4/5 MRC grade weakness. Sensory examination was normal although he had left sided neglect. Bilateral Babinski signs were present, and he had a prominent grasp reflex. He was unable to walk unaided.

Laboratory testing showed normal acute phase reactants, thyroid function tests, and an autoimmune screen. Tests for Lyme, Borrelia, Syphilis, cryptococcus and HIV were negative. The CSF showed 4×10^6/L WBC, no red cells, protein of 34 g/dL, and normal cytology (2 lumbar punctures). Paraneoplastic antibodies were negative. CMV and EBV PCR were negative. An EEG showed generalized intermittent slowing suggestive of a diffuse encephalopathy and decreased background in the right hemisphere, suggestive of a structural lesion.

Radiology. MRI showed areas of high signal on FLAIR imaging (Figure 1A) in the bilateral frontal and parietal white matter consistent with an infiltrative process. Gadolinium enhanced images showed patchy enhancement indicating blood brain barrier disruption (Figure 1B). A 4-vessel cerebral angiogram showed no evidence of vasospasm to suggest a CNS vasculitis. An FDG-PET scan showed multi-focal areas of increased uptake, suggestive of actively metabolic structural lesions (Figure 2). The signaling in the FDG-PET (Figure 2, arrow) correlates with the area of enhancement on MRI (Figure 1B, arrow). There was diffusely decreased uptake in both hemispheres including the subcortical nuclei, suggestive of widespread cortical dysfunction. There were no focal metabolic defects to suggest infarction or severe ischemia. There was preserved activity in the posterior parietal, parieto-temporal cortices and frontal lobes; these findings did not support an Alzheimer-type or frontal dementia.

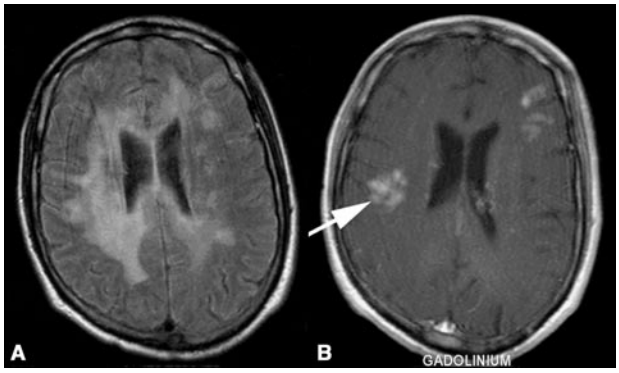

Figure 1.

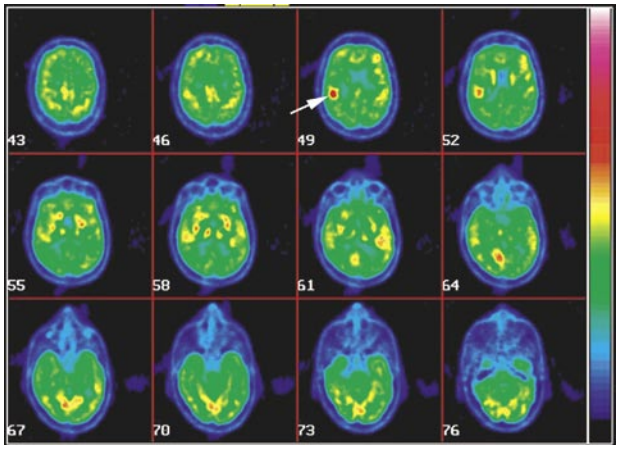

Figure 2.

Microscopic description. A brain biopsy was performed. The specimen showed diffuse infiltrates of large malignant cells with large nuclei and prominent nucleoli (Figure 3). These cells were immunoreactive with antibodies to CD20 (Figure 4).

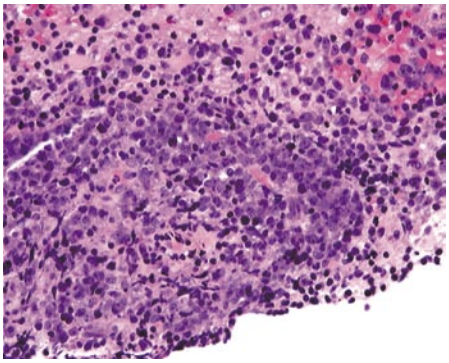

Figure 3.

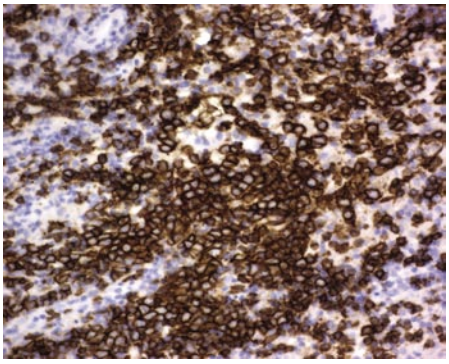

Figure 4.

Diagnosis. Primary CNS Lymphoma (large B-cell type)

Discussion. Primary CNS lymphoma is a malignant extra-nodal lymphoma confined to the CNS. Peak incidence in non-AIDS patients is in the fifth to the seventh decade. The presentation is usually with a progressive cognitive decline and focal deficits. Progressive dementia and cognitive impairment is a feature of the slow infiltrative and diffuse nature of the tumor.

Radiographically, multifocal lesions in the supratentorial white matter are usually present. CT shows single or multiple isodense or hypodense lesions that enhance. Surrounding edema is usually less than that expected for a glioma or metastasis. MRI shows multiple enhancing lesions in T1 weighted images and hyperintense tumor and edema in T2 weighted images (4). The most common locations involved are the frontal lobes, basal ganglia and periventricular regions. FDG-PET shows areas of increased glucose uptake corresponding with metabolically active tumor.

Diagnosis is by brain biopsy. Recent use of steroids may decrease the diagnostic yield. Microscopic appearance shows an angiocentric growth pattern with cuffs of tumor cells around cerebral blood vessels. Tumor cells invade the surrounding brain tissue from these perivascular cuffs. There is no formation of follicles in contrast to non-CNS lymphoma. Cytological analysis shows large lymphoid cells of B-cell lineage. There is expression of B cell markers CD19, CD20, and CD79a. Variable numbers of T lymphocytes, macrophages, activated microglia and reactive astrocytes may be seen. Necrosis may be present, particularly if there was previous treatment with steroids. T cell lymphoma is rare but may occur (2% of cases) (3).

The molecular pathogenesis of the abnormal B cell is not fully understood. Intracerebral superantigens that have been associated with a variety of infectious agents may play a role in the expansion and persistence of abnormal B cells (1). Specific viruses that have a predilection for persistence within the CNS, such as Polyomavirus and Herpesviruses, have been proposed as possible candidates (4). Epstein Barr virus is particularly associated with CNS lymphoma in AIDS patients (1). HCV has been associated with several types of non-Hodgkin's lymphoma, as a trigger to B-cell clonal expansion, but this has not been shown in primary CNS lymphoma (5).

Histological subtype does not correlate with prognosis (2). Median survival without treatment is 2-3 months and with steroids is 4-5 months. Survival can be longer with chemotherapy and/or radiation. In our case, the patient responded well to two courses of intra-arterial methotrexate with improvement in MRI appearance of the lymphoma and has survived 8 months since biopsy.

In summary, the clinical presentation of progressive cognitive impairment along with several focal findings on neurologic examination suggested bilateral hemispheric involvement. EEG, MRI, and PET scans confirmed our clinical findings. The differential diagnosis for this presentation is limited to demyelinating disease such as multiple sclerosis, vascular dementia, and infiltrating neoplasm such as glioblastoma multiforme or lymphoma. Diagnosis was made by morphologic and immunohistochemical analysis of brain tissue.

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