

A 19-YEAR-OLD MALE WITH GENERALIZED SEIZURES, UNCONSCIOUSNESS AND A DEVIATION OF GAZE

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CLINICAL HISTORY AND IMAGING

A 19-year-old previously healthy man was admitted in an unconscious state with a conjugate deviation of gaze to the right. Having been intubated and ventilated, he suffered a series of generalized seizures. Cranial MRI FLAIR showed a slightly enhanced periventricular edema zone in the white matter adjacent to the posterior horn (Figure 1).

After discontinuing sedation, the patient had no focal neurological deficits on dexamethasone alone. A stereotactic biopsy revealed perivascular lymphoplasmacellular infiltration of mainly small lymphocytes with a prevalence of the B type. A few scattered B blasts were seen as well as numerous plasma cells monotypically expressing the immunoglobulin (Ig) lambda but rarely the kappa light chain. The growth fraction measured by Ki67 expression did not exceed 5%. Arterial walls were thickened and hyalinized. There were no signs of vasculitis or encephalitis. The four different pathologists who examined the material supposed a low-grade B cell lymphoma with plasmacellular differentiation.

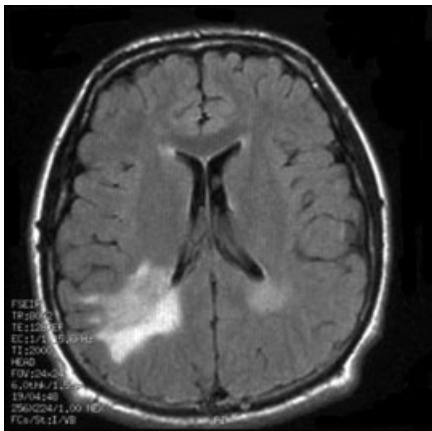


Figure 1.

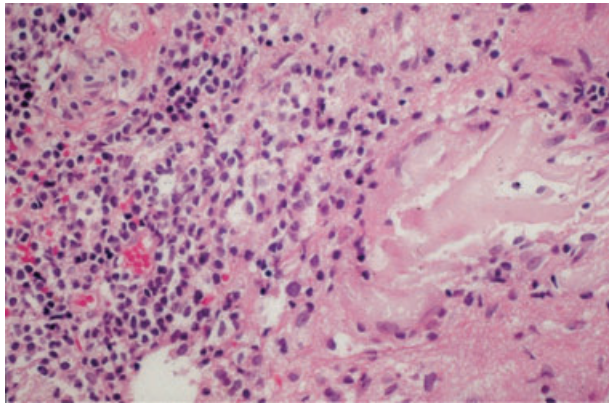


Figure 2.

The CSF examination showed 3.3 cells/ μ l and an elevated protein of 0.62 g/l. Oligoclonal bands were not observed in the CSF protein electrophoresis, and only polyclonal Ig heavy chain rearrangements were ascertained by CDIII-region PCR. No systemic lymphoma manifestations were found in the clinical examination or on chest and abdominal CT scans. A bone marrow (BM) biopsy did not show a lymphoma infiltration or an increase in plasma cells (5%). Immunoprecipitation showed no monoclonal gammopathy in blood or urine. Kidney and liver function parameters, echocardiography and ECG were normal. A mucosal biopsy taken from the lip revealed no pathological findings. After 3 cycles of systemic methotrexate chemotherapy he suffered another generalized seizure. Carbamazepine was started, and no further seizures occurred. Since MRI showed no change in lesion size, another

stereotactic biopsy was performed. Chemotherapy was stopped and MRI scans after 3 and 6 months demonstrated a slight decrease in lesion size. The patient's condition is still stable 24 months after the onset of the first symptoms.

MICROSCOPIC DESCRIPTION

Histological examination revealed lymphocellular infiltration (Figure 2) containing an equal number of B and T cells as well as a few plasma cells (L26, Figure 3A). The expression of the Ig lambda light chain (Figure 3B) was predominant compared to kappa light chain (Figure 3C). The proliferation rate was 1–3%. We observed abundant amorphous eosinophilic material (Figure 2A) without double refraction or congophilic properties. Therefore it was not amyloid. However, the material stained positive for the lambda light chain (Figure 3D) whereas it was negative for kappa.

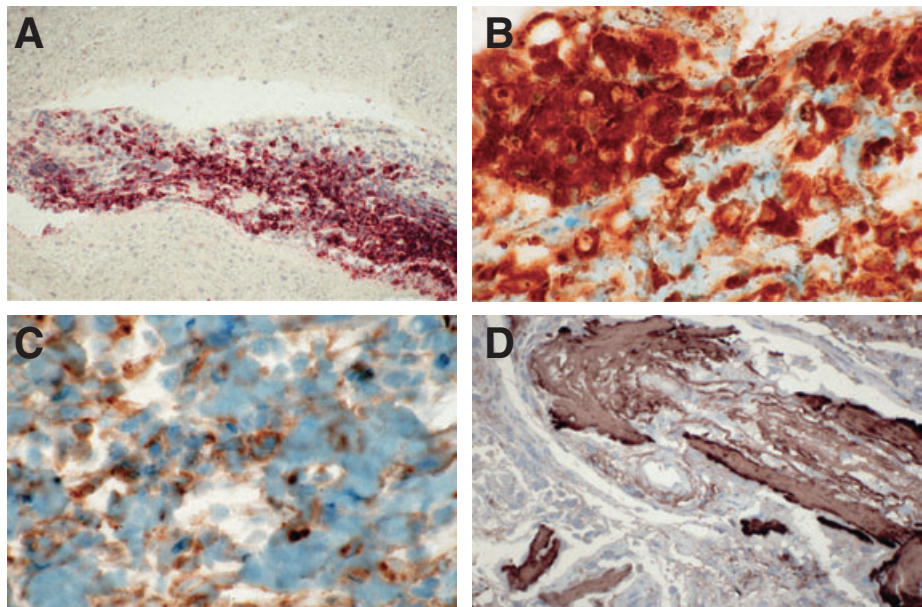


Figure 3.

DIAGNOSIS

Light chain deposition disease (LCDD) of the brain following cerebral low-grade lymphoma.

DISCUSSION

MIDD are defined by tissue deposits of monotypic Ig heavy or light chains, the major cause being a clonal expansion of Ig-secreting plasma cells. The most common form of MIDD is light chain-derived amyloidosis (AL), characterized by Congo red staining of the deposits and green birefringence under polarization microscopy caused by the β -pleated sheet arrangement of amyloid protein. Electron microscopy visualizes nonbranching fibrils with an accompanying pentagonal glycoprotein (P component). Immunohistochemically, the deposits stain monotypically for κ or λ chains, the latter predominating (1). In contrast, the less frequently recognized LCDD and the combined light and heavy chain deposition diseases (LHCDD) are characterized by deposits of non-fibrillary, amorphous material without β -pleated sheet configuration, which makes them Congo-red-negative. Amyloid P or apolipoprotein E is not detectable. In LCDD, κ deposits are overrepresented compared to λ ones (2).

The mechanisms leading to light-chain aggregation to either amyloid or non-fibrillary structures are not fully understood. The observation of both amyloid and light-chain deposits in the same patient suggests that the aggregation pathway is strongly affected by environmental conditions in addition to sequence properties (3).

LCDD usually involves the kidneys, but frequently also the liver, heart and nerves and occasionally the joints. Thus, the clinical picture comprises nephrotic syndrome, renal failure, congestive heart failure and, less frequently, liver-related coagulopathy, arthropathy and peripheral neuropathy (2, 4). Plasma cell dyscrasia with monoclonal gammopathy is present in the majority of cases. Though a systemic manifestation was not found in our patient, it cannot be ruled out, since monoclonal light chains may only be detectable intermittently and at low concentrations in serum and/or urine. Moreover, up to 30% of the LCDD patients do not have a

demonstrable lymphoplasmacytic disease (2).

This is the first published report on LCDD exclusively confined to the brain. The reason for this unusual LCDD site remains unclear, and it is likewise unknown why the disease is restricted to the brain. The most probable explanation is that LCDD originated from the low-grade cerebral lymphoma diagnosed 3 months earlier. PCNSL is a rare entity which accounts for maximal 2% of primary brain tumors with the low-grade subtype comprising approximately 20% in recent publications (5). The ability to produce Ig light chains which aggregate as amyloid has been demonstrated in a few cases (6, 7). Conversely, occasional deposits of amyloid-like, Congo-red-negative material in areas surrounding primary CNS lymphoma (PCNSL) were described by Jellinger et al. (8). In other respects light chain deposits were found in the choroid plexus and pituitary gland of two patients with plasmacytoma and systemic LCDD pituitary gland as well as in the choriocapillaris and the Bruch's membrane of another patient, attributed to plasmacytoma and systemic LCDD (9). However, the first report does not state whether the deposits were found in the neurohypophysis.

In our patient, the low-grade lymphoplasmacytic cerebral B-cell lymphoma probably led to the production of light chains which did not aggregate as amyloid but formed light chain deposits. According to this hypothesis, LCDD of the CNS is a neoplasm of an Ig light chain-producing B-cell clone capable of terminal differentiation.

LITERATURES

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CASE OF THE MONTH: ABSTRACTS

October 2005. This 48 year-old male presented with sudden right sided weakness and hypertension, and on CT was found to have a deep left hemispheric intracerebral hematoma. There were accompanying bilateral hypointensities in the occipital lobes, unchanged 1 day later, when expansion of the hematoma and uncus herniation resulted in death. The past medical history included liver transplantation followed by long term cyclosporin, features of thrombotic thrombocytopenic purpura (TTP) attributed to cyclosporin, type 1 diabetes mellitus and acute renal failure attributed to diabetic nephropathy. There was a 2-month history of hypertension poorly responsive to therapy. The occipital lobes at autopsy showed focal cortical hemorrhages with bilateral discoloration of white matter sparing subcortical zones. Microscopy showed white matter pallor with parenchymal cysts, enlarged perivascular spaces and focal acute hemorrhages consistent with edema secondary to acute hypertension. Cortical hemorrhages were associated with intravascular thrombi and fibrin exudates, as well as an accompanying microinfarct, attributed to TTP. The occipital pathology reflects the posterior leukoencephalopathy syndrome (PLS) combined with cortical lesions of TTP. PLS is usually diagnosed radiologically by occipital hypointensities, and is reversible, so that autopsy pathology is rarely examined. TTP may predispose to the development of the PLS in certain cases.

November 2005. A 35-year-old woman presented with one month's history of progressive bilateral leg weakness and altered sensation. There had been no pain. She had noted urinary frequency and constipation in the previous two weeks. On examination, the patient had diffuse lower extremity weakness (2-3/5), with a T6 sensory level to pain and temperature sensation. MRI demonstrated a T4-5 intradural mass ventral to the spinal cord, with an enhancing dural tail, consistent with meningioma. At surgery an intradural, extramedullary, firm, black neoplasm was encountered, which invaded the ventral dura and elevated and distorted the spinal cord. The mass was removed, leaving only microscopic invasion of the ventral dura. There was no bone invasion. Serial sections revealed a homogeneous black tumor without

necrosis. H&E stained sections showed an occasionally fascicular tumor of melanocytes and small round blue tumor spindle cells with melanin pigmentation and 1-2 mitotic figures per 10 high-powered fields. The nuclei are generally oval-shaped and elongated, with prominent nucleoli. Necrosis, hemorrhage, and nuclear and cellular pleomorphism are not present and mitotic figures are rare. Immunohistochemical staining was positive for S-100 and HMB-45. MIB-1 labeling averaged 1-2%. A diagnosis of primary meningeal melanocytic tumor was made. Primary meningeal melanocytic tumors (PMMTs) are rare; fewer than 100 cases have been described. PMMTs of the CNS consist of a spectrum of tumors ranging from well-differentiated melanocytoma to its overtly malignant counterpart, melanoma. Intermediate grade melanocytomas (IMGs) are the least common variant, comprising about 10% of PMMTs reported. IGMS occur in the spinal leptomeninges and intracranially in approximately equal proportions. IMGs are more cellular than the well-differentiated variant, with 1-3 mitotic figures per 10 HPFs and MIB-1 labeling of <6%.¹ By contrast, melanomas contain more mitotic figures (3-15 per 10 HPF) and MIB-1 labeling rates up to 15%.¹ Once metastasis, including drop metastasis from pigmented medulloblastomas, have been excluded, the differential includes pigmented meningiomas and schwannomas (solitary or as part of Carney complex), as well as other pigmented CNS tumors such as ependymoma and pineoblastoma and systemic diseases such as lymphoma... For primary CNS melanocytic neoplasms, complete tumor resection is preferred, as it leads to cure of well-differentiated and intermediate-grade melanocytomas and most melanomas. Radiotherapy is recommended for incomplete resection of IMGs and melanomas; the recurrence potential of low-grade melanocytomas is less clear and watchful waiting may be employed, since recurrent tumors may be treated surgically prior to radiation. Two months after surgery, the patient had normal sensation and strength. She was given focused radiotherapy to the region of the ventral thecal sac to 40 cGy. At one year following surgery, the patient's neurological examination is normal and she remains free of residual disease by MR examination.

December 2005. Light chain deposition disease (LCDD) is a form of monoclonal

immunoglobulin deposition diseases (MIDD) which in contrast to light-chain derived (AL) amyloidosis is characterized by non-congophilic, non-fibrillary monoclonal protein deposits. Systemic organ deposits are common with the kidney being a major target organ. A clonal lymphoplasmacytic proliferation, e.g. plasmacytoma, is present in the majority of cases.

Here we report on a 19-year-old male who presented with generalized seizures and an enhancing white matter lesion on MRI scans. A stereotactic brain biopsy revealed a low-grade B cell lymphoma with plasmacellular differentiation as well as lambda light chain deposits without birefringence under polarized microscopy. No systemic lymphoma manifestations or systemic light chain deposits were found, nor was a monoclonal gammopathy detectable in serum and urine.

After systemic chemotherapy with three courses high-dose methotrexate the size of the lesion and the condition of the patient have remained stable for 24 months now.

This is the first description of cerebral LCDD developing without systemic disease in conjunction with the diagnosis of a cerebral low-grade B cell lymphoma. We present the clinical, laboratory and radiological findings and discuss the pathogenesis of this unusual LCDD manifestation.