Fatal B-cell Lymphoma Following Chronic Lymphocytic Inflammation With Pontine Perivascular Enhancement Responsive to Steroids

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In 2010, Pittock et al1 identified a new inflammatory disease entity of the central nervous system (CNS) presenting with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). We report on a well-documented patient who presented with clinical, radiological, and pathological characteristics of CLIPPERS and who had an unfavorable outcome.

We present the clinical, imaging, laboratory, brain biopsy, and autopsy findings of a 57-year-old male patient with CLIPPERS who repeatedly responded well to high-dose corticosteroids. During follow-up, however, treatment failed, and he had a biopsy-confirmed diagnosis of lymphomatoid granulomatosis that evolved into fatal B-cell lymphoma of the central nervous system.

The clinical and imaging features of CLIPPERS include an abundance of differential diagnoses, and the follow-up periods of the described cases classified as CLIPPERS have been limited. Therefore, the question remains whether CLIPPERS is an actual new disease entity or represents a syndrome that includes different overlapping diseases and their prestages. Our case report shows that a typical presentation of CLIPPERS does not uniformly imply a favorable outcome, even when timely treatment regimens have been given.

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Thorax and abdomen were entirely normal. Cerebrospinal fluid samples revealed mild pleocytosis but no atypical or malignant cells, and no evidence for intrathecal IgG synthesis. Cerebrospinal fluid immunocytochemistry showed mainly T lymphocytes and, in the absence of B cells, no hint of B-cell monoclonality. The patient was treated with 1000 mg of intravenous methylprednisolone sodium succinate for 3 consecutive days, which lead to a substantial improvement of clinical symptoms, especially with regard to diplopia and facial hypoesthesia. In addition, the inflammatory changes detected in the brain on MRI scans regressed. However, 6 weeks later, his symptoms worsened, with increasing gait ataxia, diplopia, dysarthria, and aphasia and with a clinical examination now also showing a seventh nerve palsy, impaired coordination, and bipyramidal syndrome. The MRI scans revealed an increased number of punctuate and curvilinear gadolinium-enhanced hyperintense white matter lesions, mainly in the pons, cerebellum, and periventricular region (Figure 1B).

Whole-body fludeoxyglucose F18 positron emission tomography showed no abnormalities, nor did extensive blood analysis. The results of serology using a chemiluminescent microparticle immunoassay were negative for Epstein-Barr virus (EBV), as were the serologic test results for herpes simplex virus, cytomegalovirus, human immunodeficiency virus, varicella zoster virus, BK virus, tuberculosis, Whipple disease, JC virus, mycoplasma, toxoplasmosis, lues, and borreliosis. The results of autoimmune screening were negative for antinuclear antibodies, anti-extractable nuclear antigens, antineutrophil cytoplasmic antibodies, cardiolipin IgG antibodies, and cardiolipin IgM antibodies. A frontal lobe brain biopsy revealed small enhancing periventricular lesions and lymphohistiocytic inflammatory infiltrates with perivascular predominance, consisting primarily of T lymphocytes and of some B lymphocytes, histiocytes, and plasma cells with no fibrinoid necrosis of vascular walls (Figure 2A). No erythrocyte extravasation was observed, ruling out the differential diagnosis of primary CNS vasculitis. Because the results of EBV analysis using in situ hybridization were negative, a diagnosis of lymphomatoid granulomatosis (LYG) was not confirmed at this stage.

The patient was readmitted and treated for 5 consecutive days with intravenous methylprednisolone (1000 mg once a day), followed by intravenous immunoglobulins. Treatment resulted in significant clinical improvement of symptoms, and MRI scans showed a dramatic decrease in the number and extent of gadolinium-enhanced lesions and in the intensity of en-
hancement, specifically in the pons and cerebellar peduncle, when compared with the previous MRI scan (Figure 1C). Two months later, the patient had to be readmitted because of severe worsening of clinical presentation with progressive dysarthria, paresis of both legs, left-sided diplopia, peripheral facial nerve palsy, dysdiadochokinesia, upgoing plantars, and gait ataxia. His symptoms improved slightly after 3 consecutive days of intravenous methylprednisolone treatment (1000 mg once a day), with further slight improvement after additional intravenous rituximab (800 mg twice a day) treatment and 60 mg of prednisone sodium phosphate orally once a day. However, after 1 month, despite continuous oral prednisone, his symptoms rapidly worsened. The latest MRI brain scan showed a pontine ringlike lesion with peripheral gadolinium enhancement and a nonenhanced center with edema, multifocal punctuate perivascular white matter lesions, and mass effect (Figure 1D). He was admitted to intensive care with impeding brain stem herniation. A second brain biopsy was performed that revealed numerous large atypical B lymphocytes positive for EBV-encoded RNA, which is pathognomonic for LYG, and diffuse large B-cell lymphoma (Figure 2B). The last treatment trial with methotrexate sodium and dexamethasone acetate failed, and intensive care treatment was de-escalated. The latter biopsy findings were confirmed at autopsy.

Discussion

According to the 2001 World Health Organization classification of tumors,6 LYG is an EBV-related angiocentric and angiodestructive disease that comprises B-cell proliferation and a reactive T-cell infiltration with uncertain malignant potential.7-9 Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids is a recently described CNS inflammatory disease with a characteristic brain pattern of punctuate and curvilinear enhancements primarily in the brain stem, especially the pons.1

With the pathogenesis of LYG still unclear, Demetrick et al10 hypothesize that LYG is a reactive or neoplastic B-lymphocyte process related to EBV antigen stimulation. González-Darder et al8 and Schmidt et al11 have suggested the possibility of a decreased T-lymphocyte immunosurveillance function due to a chronic or transient defective T-cell function leading to the latent arousal of EBV-infected B-lymphoid cells. This results in the derangement of both the physiological relationships between T and B cells and in the derangement of the regulation of the tumor suppressor genes and/or oncogenes of these cells, resulting in an uncontrolled lymphoproliferation.8,11 We hypothesize that CLIPPERS is the possible cause of this initial chronic or transient T-cell dysfunction, leading to the EBV antigen stimulation as described by Demerick et al.10

Considering the core symptoms and signs of CLIPPERS described by Simon et al,2 our patient presented with almost identical features. Although in the original description by Pittcock et al1 some patients did suffer from cranial neuropathy, as did our patient, it is uncertain whether this is a characteristic feature of CLIPPERS. The MRI scans showed numerous, primarily unilateral, punctuate lesions in the pons and cerebellum of decreasing intensity with increasing distance from the brain stem. This asymmetry may be considered a somewhat atypical feature because others have described a more symmetrical distribution of enhancing lesions.2 However, MRI scans showing an asymmetric distribution of enhancing lesions have been described for a single patient at initial presentation.1 This asymmetry, in combination with cranial neuropathy at presentation, might be a red herring for CLIPPERS and its prognosis. Our patient initially showed a prompt and significant clinical and radiological response to corticosteroids as well, and, histopathologically, a white matter–based perivascular lymphohistiocytic infiltrate composed primarily of T lympho-
Encountered lymphocytes without fibrinoid necrosis, erythrocyte extravasation, or other features of vasculitis could be determined. These histopathological features are similar to those described by Pittack et al and are considered by some to be part of the core features of CLIPPERS. Because CLIPPERS had not been described yet at that time, no such diagnosis was made. Over time, the clinical presentation and the MRI scans showed features that went beyond the classical findings described for CLIPPERS. As described by Lucantoni et al and Patsalides et al, brain lesions may evolve into a ringlike enhanced mass with a non-enhancing center, as it did with our patient. Furthermore, the brain biopsy and autopsy eventually confirmed the presence of numerous large atypical B lymphocytes positive for EBV-encoded RNA, which some authors describe as a pathognomonic feature of LYG.

In conclusion, both LYG and CLIPPERS are rare diseases that are difficult to diagnose. Herein, we attempt to contribute to the clinical understanding of both neuroinflammatory diseases by introducing a new hypothesis linking the newly described CLIPPERS to LYG.

We speculate that CLIPPERS could possibly be an early phase of LYG, at least in a proportion of cases, progressing to a manifestation of a latent EBV infection or to a primary EBV infection. Long-term follow-up of these patients is required, and the inability to improve with steroid treatment may be a poor prognostic sign.

REFERENCES