CLIPPIERS With Chronic Small Vessel Damage: More Overlap With Small Vessel Vasculitis?

In 2010, Pittock et al (1) published a seminal report on an entity they entitled “Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPIERS).” After this, other reports of the entity quickly appeared (2–22) (Table). A recently presented abstract reviews several more unpublished non–English language cases (19). Despite this, most reports have emphasized neuroimaging or clinical features and neuropathologists may not be familiar with the syndrome.

As discussed in commentaries by Kira (23), and Keegan and Pittock (24), the essential feature of the disease is seen on magnetic resonance imaging (MRI) scans. These show punctate and curvilinear gadolinium enhancement that “peppers” the pons; the enhancement is almost always symmetric (with only 1 of 8 asymmetric in the original series [1] and 1 asymmetric in a recent case report [17]). Signal abnormalities often extend into contiguous cerebellum, brainstem, or even thalamus and cerebral cortex, as emphasized by others after the original report (3, 4, 10). Simon et al (10) even suggested a nomenclature modification from “pontine” to “pontocerebellar” to reflect the more widespread features.

Clinically, patients present with fluctuating brainstem symptoms and show response to steroids, although it has become increasingly clear that relapses are frequent (8) and immunosuppressive therapy often needs to be prolonged; nonsteroidal drugs such as cyclophosphamide, azathioprine, or rituximab have been required (18, 19). Stereotypic neuroimaging features were felt from the initial report to obviate the need for brain biopsy (1), leading to fewer histologic than clinical/neuroimaging descriptions of the syndrome (Table). Nevertheless, neuropathologic features of CLIPPIERS, even when biopsied from nonpontine sites (Table), have been fairly uniform. Most cases have shown perivascular and parenchymal lymphocytic collections associated with macrophages, microglia, and occasionally plasma cells or neutrophils; true tight granulomas and demyelination are not present (Table). When lymphocytic subsets have been phenotyped, CD4-positive cells were more frequent than CD8-positive lymphocytes or CD20-positive B cells (4, 10).

The original authors carefully considered, and excluded on clinical-serologic-histologic grounds, several possible confounding conditions, particularly Bickerstaff brainstem encephalitis, neuro-Behçet disease, and Sjögren syndrome but also neurosarcoidosis, Langerhans cell histiocytosis, and paraneoplastic brainstem encephalitis (1). Bickerstaff brainstem encephalitis was thought unlikely because of the absence of antecedent viral infection or microglial clusters; several subsequent CLIPPIERS patients have taken the opportunity to further provide negative testing for the GQ1b IgG antibodies coassociated with Bickerstaff brainstem encephalitis (5, 7, 14). Workup for Sjögren syndrome (when performed) has been negative, although, of the 5 patients in the series by Simon et al (10), one had biopsy-proven chronic lymphocytic sialadenitis and one had lymphocytic conjunctival infiltrates without granulomas. Salivary gland biopsy in the case reported by Biotti et al (11) was normal. Other unusual individual patients with otherwise radiographically typical CLIPPIERS have manifested elevated IgE (4, 12), peripheral nerve abnormalities on nerve conduction studies (12), multiple sclerosis with onset of CLIPPIERS after withdrawal of drug therapies (15, 21), temporal association with influenza vaccination (13), primary central nervous system lymphoma (9, 17), or even glioma-like biopsy features (6). Kira (23) has questioned whether CLIPPIERS is a single disease or a syndrome and Keegan made the critical point that until specific markers are identified for CLIPPIERS, it may be impossible to answer the question (24).

We recently encountered a case that adds new information, that is, that small vessel injury, which was chronic in our case, can be seen in at least a subset of radiographically typical CLIPPIERS patients. We put our case in the context of the fact that, since the original description emphasizing the absence of vasculitis (1), Simon et al (10) reported focal transmural lymphocytic inflammation in 3 of 5 cases and axonal injury in 3 of 3 assessable cases; the very recent report by Buttmann et al (16) showed overlap with angiitis based on digital subtraction angiography and biopsy findings.

A 49-year-old woman with no significant past personal or family medical history and an absence of chronic hypertension presented with 3 weeks of left facial numbness, dysphagia, dysarthria, and right upper extremity weakness associated with occipital headache. Neurologic examination further demonstrated decreased sensation in the V1 to V3 distribution of the left cranial nerve V, 4/5 weakness in the right upper extremity, and a mildly ataxic gait.

Magnetic resonance imaging scan of the brain with and without gadolinium contrast demonstrated a homogeneously enhancing left cerebellum/pontine angle mass (thought to be meningioma) and abnormal T2 hyperintensities “pepper” the pons associated with enhancement (Fig. 1A). Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis (94% lymphocytes), normal glucose, normal protein, and normal cytology with small- and medium-sized lymphoid cells. Workup was negative for syphilis (CSF VDRL), Lyme disease, viruses by CSF polymerase chain reaction (PCR) testing (cytomegalovirus, herpes simplex, HHV-6, varicella zoster, JC viruses), human immunodeficiency virus 1/2, and fungi. Serologic testing was negative for the following antibodies: anti-DNA, anti-centromere, anti–N-RNP, anti-Smith, anti-SSA, anti-SSB, anti-nuclear, C-anti-neutrophil, P-anti-neutrophil, rheumatoid factor, neumyelitis optica (repeated twice), and paraneoplastic panel. Also negative or normal were tests for lupus anticoagulant, Russell viper venom, angiotensin converting enzyme, and vitamin B12. Complement components (C1 esterase inhibitor, C3a, C3c, C4, C5a, complement 2) were
FIGURE 1. (A) Magnetic resonance imaging (MRI) with gadolinium at time of clinical presentation shows curvilinear and speckled contrast enhancement symmetrically distributed in pons and radiographically typical for CLIPPERS. Note the incidental left cerebellopontine angle mass. (B) MRI with gadolinium after first round of steroids shows significant resolution of the neuroimaging abnormalities; the patient was also significantly clinically improved at this time. (C) MRI with gadolinium at the time of clinical relapse of symptoms several months after her steroid taper shows recurrence of the pontine abnormalities. (D) Brain biopsy showed multifocal white matter small vessels with perivascular and vascular wall inflammation composed of small lymphocytes without cytologic atypia (top; hematoxylin and eosin, original magnification, 600×) that were predominantly CD3-positive T-cell lymphocytes (bottom; original magnification, 600×). Individual T cells in parenchyma were also noted. (E) CD68-immunopositive perivascular macrophages and parenchymal microglial cells were present, although no tight microglial clusters were seen (original magnification, 600×). (F) Other vessels showed more chronic injury with hyalinization and minimal inflammation, resulting in fibrosis, particularly of the adventitia (hematoxylin and eosin, original magnification, 600×). (G) Hyalinized small vessels showed scant perivascular pigment (top, arrowhead), which was negative for iron (bottom; Perl iron stain, arrowhead, original magnification, both 600×). (H) Chronically injured hyalinized small vessels showed surrounding increased concentrations of macrophages but no cavitation or extensive demyelination (immunostaining for CD68 with light hematoxylin counterstain, original magnification, 400×). (I) After cyclophosphamide, CellCept, and prednisone treatment a second time, her neuroimaging and clinical abnormalities regressed, as seen on MRI with gadolinium.
<table>
<thead>
<tr>
<th>Reference cited, Emphasis of Report</th>
<th>No. Cases Reported</th>
<th>No. Cases With Biopsy, Site</th>
<th>Neuropathologic Features</th>
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<tbody>
<tr>
<td>(1) Seminal study</td>
<td>8</td>
<td>4 (1 pons, 3 Cblm)</td>
<td>White matter perivascular and more diffuse lymphocytic infiltrates, T cells (CD3⁺) &gt; B cells (CD20⁺); moderate numbers CD68⁺ macrophages and microglia without granulomas, vasculitis, vascular injury; myelin intact</td>
</tr>
<tr>
<td>(2) Neuroimaging: severe pontine inflammation, features more recognizable on post-Rx MRI, increased blood flow on DWI, eventual severe shrinkage of pons</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
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<td>(3) Cerebellar and subcortical cerebral white matter more abnormal on neuroimaging than pons</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>(4) Extrapontine lesions, with 2 thalamic and 1 spinal cord; 2 of 3 cases with marked elevation of serum IgE</td>
<td>3</td>
<td>3 (1 patient with biopsy of thalamus X2; 2 in Cblm)</td>
<td>Extensive IHC, PCR analyses for B/T-cell clonality on paraffin-embedded tissue (IgH, T-cell receptor gamma gene rearrangements) = polyclonal</td>
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<td>(5) Onconeural Abs negative, good response to steroids</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>(6) First case recurred when steroids tapered; second case had biopsy, thought to be glioma; did not respond to steroids</td>
<td>2</td>
<td>1 (pons)</td>
<td>Biopsy (no on Rx) showed atypical enlarged astrocytes with abundant cytoplasm, fibrillary background, Rosenthal fibers, cytologically bland T cells concentrated around normal vessels; no vasculitis or lymphoma</td>
</tr>
<tr>
<td>(7) Follow-up with MRS with recovery of NAA/Cr levels in pons and thalamus after treatment</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>(8) Teaching neuroimage; recurrence after steroid discontinuation</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>(9) Brain biopsy critical; second biopsy showed B-cell lymphoma</td>
<td>1</td>
<td>1 (pons biopsied X2)</td>
<td>First biopsy: perivascular lymphocyte infiltrates (pre-steroid Rx), no lymphoma or LYG. Second biopsy (after development of pontine necrosis by neuroimaging): B-cell primary CNS lymphoma (no gene rearrangement studies)</td>
</tr>
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<td>(10) Longer follow-up: pontocerebellar atrophy occurs early even with prompt treatment; may get cognitive deficits &amp; cerebral atrophy; 1 case with chronic lymphocytic sialadenitis on biopsy; 1 with lymphocytic conjunctival infiltrate</td>
<td>5</td>
<td>5 (4 Cblm, 1 basal ganglia)</td>
<td>Extensive IHC analysis (CD3⁺ &gt; CD20⁺, CD4⁺ &gt; CD8⁺ cells; no other IHC in situ positivity; white matter perivascular and parenchymal lymphohistiocytic infiltrates, reactive gliosis, no neutrophils or eosinophils, rare plasma cells, focal transmural lymphocytic infiltration in vessel walls in 3/5 cases without fibrinoid vascular necrosis, leukocytosis, fibrin thrombi</td>
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<tr>
<td>(11) Dramatic improvement with steroids; onconeural Abs, tumor markers negative; accessory salivary gland biopsy normal</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
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</table>
(12) First patient from east Asia; elevated IgE levels, history of allergies; NCS suggested demyelinating mononeuropathy multiples

(13) Followed influenza vaccination

(14) Additional neuroimaging features of brainstem mass effect in 5, myelitis in 3, closed ring enhancement in 1 (includes 1 previously published case)

(15) CLIPPERS in an MS patient after natalizumab withdrawal

(16) Overlap with vasculitis; digital subtraction angiography showed focal beading and narrowing of cerebral arteries; onconeural Abs and pre-biopsy vasculitis workups negative

(17) Fatal B-cell lymphoma

Neuroimaging pontine features relatively asymmetric

(18) Need for prolonged immunosuppressive Rx, review of Rx and relapse in previously published cases, onconeural Abs negative

(19) No new primary cases but included non-English language papers and cases presented as recent abstracts

(20) 12-month follow-up with patient on azathioprine; onconeural Abs negative

(21) CLIPPERS in MS patient after intravenous methylprednisolone

(22) Susceptibility and perfusion-weighted neuroimaging features

Abs, antibodies; Cblm, cerebellum; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; DWI, diffusion-weighted imaging; EBV, Epstein-Barr virus; IHC, immunohistochemistry; LYG, lymphomatoid granulomatosis; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MS, multiple sclerosis; NA, not applicable; NAA/Cr, N-acetylaspartate-to-creatine ratio; NCS, nerve conduction study; PCR, polymerase chain reaction testing; Rx, therapy; +, immunopositive.
The patient was begun on dexamethasone 10 mg intravenously every 6 hours for 3 days and transitioned to oral prednisone 80 mg, with a slow taper over 8 weeks. After 3 days of steroid intravenous therapy, her symptoms and her neurologic examination dramatically improved. Nine weeks later, after the patient had been tapered to 20 mg of oral prednisone daily, her MRI showed resolution of neuroimaging abnormalities (Fig. 1B).

She did well until 2 months after this (4 months after presentation), when she again developed recurrent headache, dysarthria, diplopia with left gaze, and painful jaw spasms at a time in which she had been off prednisone entirely for 2 weeks. Neurologic examination was significant for dysarthria, mild left VI nerve palsy, decreased sensation of the left face, and bilateral dysmetria. Magnetic resonance imaging now showed recurrence, and even greater severity, of her pontine neuroimaging abnormalities (Fig. 1C). A small left frontal enhancing lesion was also noted and targeted for biopsy.

Biopsy of the left frontal cortex, including dura, cortex, and underlying subgyral white matter, was performed 3 days later. Tissue was evaluated by immunohistochemistry for CD3, CD68, β-amyloid (all Ventana, Tucson, AZ), CD20 (BioCare, Concord, MA), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP) (both from Dako, Carpinteria, CA), neurofilament (2F11, Cell Marque, Rocklin, CA) immunohistochemistry; Luxol fast blue–periodic acid-Schiff (LFB-PAS), trichrome, Perl iron stain histochemistry; and in situ hybridization for Epstein Barr virus (EBER) (Ventana).

Dura and cortical gray matter were unremarkable, and specifically cortex showed no neuronal loss, microglial clusters, vascular hyalinization on trichrome stain, or vascular amyloid on beta-amyloid immunohistochemistry. Anti-CD3 immunohistochemistry for T-cell lymphocytes revealed only rare individual cells around normal–appearing small blood vessels in the deeper cortical layers.

On the other hand, subgyral white matter contained multifocal small vessel non-neoplastic perivascular and vascular wall lymphocytes, narrowing but not fully occluding lumens (Fig. 1D, top). Perivascular lymphocytes were predominantly CD3-positive T cells, as were individual parenchymal lymphocytes (Fig. 1D, bottom), whereas smaller numbers of cytologically normal, CD20-positive, EBER-negative B cells were largely confined to perivascular regions. CD4-positive lymphocytes predominated over CD8-positive lymphocytes in both parenchyma and perivascular regions. CD68-positive perivascular macrophages as well as individual parenchymal microglia were seen, without microglial nodule formation (Fig. 1E).

The most unique feature of these biopsies was the striking multifocal small vessel hyalinization confined to white matter (Fig. 1F, G, top). Vessels were concentrically thickened, negative for PAS deposits (as might be seen in CADASIL) and of smaller caliber than damage caused by arteriosclerosis (the patient did not have a clinical history of hypertension). Perivascular pigment deposits were focally identified but were negative for iron (Fig. 1G, bottom). The largest concentration of macrophages was identified adjacent to the most severely damaged small blood vessels (Fig. 1H) but was not associated with cavitation of adjacent tissue or severe demyelination. Indeed, only focal myelin pallor was seen in these areas of macrophage influx adjacent to the most severely hyalinized small blood vessels by either LFB-PAS histochemistry or MBP immunohistochemistry. Given the modest myelin pallor, not surprisingly, the macrophages contained only small amounts of PAS-positive, but not LFB-positive, debris.

Neurofilament immunohistochemistry verified rare axonal swellings but little or no axonal loss in these same areas of perivascular myelin pallor; axonal swellings were not seen throughout the white matter. Immunostaining for GFAP highlighted diffuse reactive gliosis without preclusion for the parenchyma surrounding most severely damaged small vessels. Polymenase chain reaction testing for monoclonality in the B- or T-cell populations by IgH and TCR-γ, respectively, was negative. The features were those of small vessel injury, especially to the perivascular adventitial area.

The patient was given 1 g of cyclophosphamide intravenously immediately after biopsy and then eventually switched to mycophenolate mofetil (Cell Cept), with titration to 1,000 mg b.i.d. orally. By 2 months after the biopsy, the patient was able to be tapered off prednisone and has remained stable since that time. Neuroimaging showed resolution of pontine enhancement (Fig. 1I) and no new lesions; most recent neuroimaging performed 4 months after the biopsy was also negative. She has not developed new clinical complaints.

This case adds to the information that, in CLIPPERS, vascular injury can occur (10, 16) and, in view of the frontal lobe location of our biopsy, further shows that the damage is widespread beyond the pontine epicenter of the disease. We also follow up on the comments of others regarding whether CLIPPERS should be “considered a prelymphoma state or a new inflammatory disease” (25) or might “show possible early monoclonal expansion of B cells” (26). Our negative results by PCR for monoclonality parallel similar negative tissue biopsy PCR studies in 2 CLIPPERS patients reported by Kastrup et al (4) and 1 reported by Ortega et al (15).

We cannot prove that the small vessel wall damage in our case was caused by vasculitis, although the vessel wall changes could be compatible with both ongoing (transmural) and late vasculitis (i.e., vessel hyalinization with maximal damage to adventitial areas). We could not attribute the vascular hyalinization to chronic hypertension because the patient did not have hypertension, and stains/immunostains for CADASIL and cerebral amyloid angiopathy were negative on the biopsy. Newer reports of CLIPPERS, particularly by Simon et al (10) and Buttmann et al (16), find that at least some cases of CLIPPERS have transmural inflammation at earlier stages of the process (Table). A final possibility, which we acknowledge but do not favor, is that our case is completely unique from previous CLIPPERS patients and the vascular hyalinization is caused by an unknown type of small vessel vasculopathy.

Although much has been made in previous reports about the absence of fibrinoid vascular necrosis in cases of CLIPPERS (Table), in our experience (and in numerous studies in the literature [27–30]), small vessel lymphocytic vasculitis almost never shows fibrinoid vascular necrosis. Rather, the definition is that of “predominantly lymphocytic inflammation.
with occasional plasma cells, extending through the vascular wall with features of vascular distortion and destruction” (30). Alrawi et al (27) and Elbers et al (28) required “two layers of lymphocytes within or around the walls of parenchymal vessels” as the definitive feature of small vessel angiitis, with criteria for probable angiitis including a stipulation that there could be structural alteration of vessel wall with or without necrosis. Certainly, our case, coupled with those of Simon et al (10) and Buttmann et al (16), meet those criteria, although our example provides the clearest evidence that long-term, and permanent, vessel wall hyalinization and distortion can be seen in at least a subset of cases with radiographically typical CLIPPERS.

B.K. Kleinschmidt-DeMasters, MD
Matthew West, MD
University of Colorado at Denver
Aurora, Colorado

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