Biopsy Avoids Overdiagnosis of CNS Vasculitis

ARTICLES BY
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WASHINGTON — Vague presenting symptoms in combination with lack of accurate tests hamper the diagnosis of central nervous system vasculitis, while likely contributing to its overdiagnosis, according to Dr. David B. Hellmann, chairman of the department of medicine and the vice dean at the Johns Hopkins Bayview Medical Center in Baltimore.

Speaking at the annual meeting of the American Neurological Association, Dr. Hellmann discussed a few common myths about CNS vasculitis—also known as primary angiitis of the central nervous system (PACNS)—and offered clinical pearls.

Myths

► **CNS vasculitis is common.** In fact, CNS vasculitis accounts for only 1% all biopsy-proven cases of vasculitis. "CNS vasculitis is one of the greatest diagnostic challenges that any of us can face," said Dr. Hellmann, who is also the executive director of the Johns Hopkins Vasculitis Center. Most of the common presenting features of CNS vasculitis are shared by a variety of other conditions. While there is a cluster of symptoms that is highly suggestive of this disease, a full range of CNS abnormalities is possible. No imaging tests are specific and even brain biopsy can be falsely negative.

► **Angiograms are sensitive and specific.** The sensitivity of magnetic resonance (MR) angiography ranges from 40% to 80%, and the specificity is quite low at around 25%. The main abnormality apparent on MR angiography is a beading pattern of alternating constriction and dilatation. Posterior circulation is less likely to be affected.

► **Stroke presentation is common.** While focal abnormalities are seen in about 50% of CNS vasculitis cases, very rarely do they present as stroke. "Focal [cerebral] abnormalities are pretty common by the time that you make the diagnosis but in retrospect, very few patients describe a strokelike presentation," said Dr. Hellmann.

►**Systemic signs are common.** "Systemic symptoms are overrated. One of the myths of CNS vasculitis is that people have fevers and many other symptoms. They may, but it's actually the minority of patients who have systemic signs," said Dr. Hellmann.

Pearls

► **Definitive diagnosis takes biopsy.** The criterion for making a possible diagnosis of CNS vasculitis is a newly acquired neurologic deficit, exclusive of other causes. A positive biopsy allows for definitive diagnosis. The diagnosis of possible CNS vasculitis is made when there is no biopsy but the clinical picture and imaging, along with the exclusion of other causes, is suggestive.

Brain biopsy is falsely negative about 25%-40% of the time. "More atrophy is biopsied in the nondominant temporal lobe," said Dr. Hellmann.

Biopsy specimens should be taken from of the leptomeninges or parenchyma to produce a greater yield. Studies suggest that biopsy is positive in 9%-36% of suspected cases. "It seems to be worth doing, as another diagnosis is often found," said Dr. Hellmann. However in 25%-35% of patients, biopsy produces no diagnosis.

► **Prescribe no cyclophosphamide without a definitive diagnosis.** "In the absence of biopsy-proven case, I get nervous about using cyclophosphamide," said Dr. Hellmann. "For someone who has biopsy-proven disease, I think that … most rheumatologists would use prednisone and cyclophosphamide," said Dr. Hellmann. For a patient who is rapidly deteriorating, 1 g/day Solu-Medrol (methylprednisolone sodium succinate) should be given intravenously for the first few days, followed by 60 mg/day for a month, then taper the dose over the next 2-6 months. Oral cyclophosphamide can be used for 3-12 months.

► **The most common presentation is insidious cognitive decline with headache.** Studies have shown that the two most common presenting symptoms are diffuse cortical dysfunction (in an estimated 95% of cases) and headache (seen in roughly 70% of cases). Associated headaches are marked by an insidious rather than thunderclap onset. Seizures are also common.

► **Lumbar puncture and MRI are sensitive but not specific.** In terms of diagnostic testing, lumbar puncture and MRI are very sensitive but sensitivity is very low. In fact, patients with CNS vasculitis may have perfectly normal-appearing MRIs. Cerebral spinal fluid (CSF) findings are abnormal in 85%-90% of cases. This includes modestly elevated protein levels and modest mononuclear pleocytosis.

In terms of imaging, MRI is much more sensitive than CT. However, there is no specific pattern to look for on MRI. ■

Speed of Onset Key to Differential

The differential diagnosis of CNS vasculitis or PACNS includes rheumatic diseases, infections, drugs, and vasculopathies, said Dr. Hellmann. In particular, consider reversible cerebral vasoconstriction (RCVS), lupus, HIV, histoplasmosis, tuberculosis, intravascular lymphoma, and cerebral amyloid angiopathy (distinguished by an average age of onset that is 30 years greater than for PACNS).

RCVS consists of a group of diverse conditions that are characterized by reversible multifocal narrowing of the cerebral arteries. The first symptom of RCVS is sudden (thunderclap), severe headaches with or without associated neurologic deficits. Drugs, such as phenylpropanolamine, pseudoephedrine, and others, are frequently behind RCVS.

RCVS and PACNS do have some distinguishing features. RCVS is more common among women, while PACNS is more common among men. RCVS is marked by a thunderclap-type headache, whereas PACNS is more insidious. Patients with RCVS have floridly positive angiograms.

Current suggestions for the treatment of RCVS include observation for mild cases, calcium channel blockers (nimodipine, verapamil), or high-dose steroids.

Papillary Dermal Edema Should Not Preclude SLE Diagnosis

BALTIMORE — Marked papillary edema may be present in patients with systemic lupus erythematosus. The finding is an accepted feature of polymorphous light eruption, but is not recognized in lupus.

After finding marked papillary dermal edema in the histopathologic specimens of four patients with systemic lupus erythematosus (SLE), a group of investigators assessed the frequency of papillary dermal edema as a histologic feature of SLE in biopsies read at University of California, San Francisco from 2000 to 2003.

The investigators—Dr. Laura B. Pincus, Dr. Timothy H. McCalmont, and Dr. Philip E. Le Boit, all of UCSF—conducted a computerized search of the UCSF dermatopathology database for cases coded as SLE, identifing 502 cases. The researchers excluded cases if the microscopic findings were suspicious for but not diagnostic of SLE or if the term "lupus" was not included in the final diagnosis. A total of 131 specimens qualified for review.

The findings were presented in a poster at the annual meeting of the American Society of Dermatopathology.

The degree of papillary edema was markedly similar to that which can be observed in sections from patients with polymorphous light eruption (PMLE).

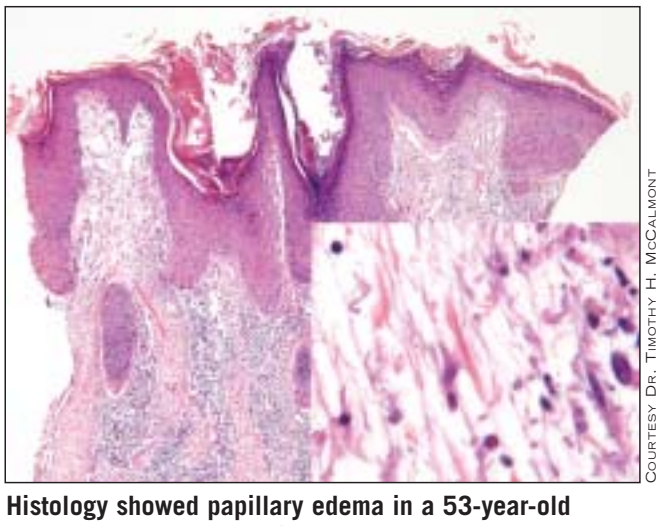
Two physicians reviewed the 131 specimens that qualified for inclusion for the presence of papillary dermal edema. In addition, the following other well-established features of SLE were scored, including:

► The presence or absence of mucin, epidermal atrophy, acanthosis, hyperkeratosis, and follicular plugging;

► Perijunctional and perifollicular alteration—rated as vacuolar alteration only, vacuolar change with necrotic keratinocytes, or vacuolar change with necrotic keratinocytes and confluent necrosis;

► Basement membrane thickening evident with routine hematoxylin-eosin staining alone or with periodic acid-Schiff, diastase-resistant staining (presence/absence);

► The density of perivascular and periadnexal infiltrate and the percentage of inflammatory cell types present.



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Histology showed papillary edema in a 53-year-old woman who presented with erythematous plaques.

Marked papillary dermal edema was present in 8% of cases. Reticular dermal mucin deposition was evident in 35% of cases and usually could be appreciated in conventional (hematoxylin-eosin) sections.

In terms of perijunctional manifestations, the majority of cases showed necrotic keratinocytes both at the epidermal-dermal junction as well as around the folliculosebaceous units. Confluent necrosis was rare. Basement membrane thickening was present in 12% of cases. Roughly half of the cases showed a modest dermal infiltrate, while half showed a relatively dense superficial and deep infiltrate. In virtually all cases, the dermal infiltrate was composed primarily of lymphocytes, with few granulocytes present.

Marked papillary dermal edema is a well-established microscopic feature of PLME. The clinical differential diagnosis of sun-induced facial plaques often includes both SLE and PMLE. "The presence of papillary dermal edema in histopathologic sections should not preclude a diagnosis of SLE," the authors concluded. In addition, "papillary dermal edema (alone) is not a reliable microscopic feature to distinguish SLE from PMLE."

Since the histopathologic sections from this patient showed papillary dermal edema, some might be tempted to render a diagnosis of polymorphous light eruption. However, the findings of this study show that papillary dermal edema can be seen in SLE as well. Vacuolar alteration also pointed to a diagnosis of SLE rather than PMLE.

Dr. Pincus is a dermatology resident; Dr. LeBoit and Dr. McCalmont are professors of pathology and dermatology. ■

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