Varicella-zoster virus claims yet another painful scalp—Giant cell arteritis

Peter G.E. Kennedy, CBE, MD, PhD, DSc
Howard L. Lipton, MD

Correspondence to Dr. Kennedy: peter.kennedy@glasgow.ac.uk

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Giant cell arteritis (GCA), characterized pathologically by inflammation in and damage to the vessel wall of the temporal arteries (TAs), is a medical emergency due to the potential for sudden blindness and several other serious neurologic complications if untreated with corticosteroids. The diagnosis is suspected in elderly individuals with a typical history, including headache, scalp tenderness, weight loss, fatigue, jaw claudication, and raised erythrocyte sedimentation rate and C-reactive protein.[1] While the characteristic histopathologic features are often detected on TA biopsy, some patients may present with a classical history of GCA but have a negative biopsy,[2] indicating either a false-negative biopsy or another etiology for the symptoms.

In this issue of *Neurology*®, Gilden et al.[3] address this issue in a landmark study in which they searched for varicella-zoster virus (VZV) antigens and DNA in TA sections from 82 biopsied cases of GCA in a population >50 years of age. Their study represents the most thorough analysis to date of TA in GCA in which at least 50 TA sections were examined per case. Their extensive study with VZV was predicated on their recent reports that some patients with suspected GCA without the diagnostic histopathology for GCA had VZV in TAs,[4] and also that VZV could be detected in histopathologically confirmed GCA.[5] Previous studies of VZV in TAs from GCA cases reported conflicting results, both negative and positive, with the latter observed when a larger number of sections were analyzed.[3] The critical question asked was how frequently VZV can be detected in proven GCA-positive cases. The critical comparison was with age-matched autopsy cases as controls. Thus, a high incidence of VZV in TAs would implicate VZV as a contributory cause of GCA, a result that would have clear implications for both the understanding and treatment of this disease.

Their findings were remarkable and provide strong evidence for the association of VZV with GCA. Using immunocytochemistry, Gilden et al. found that 61/82 (74%) GCA-positive cases contained VZV antigen, mostly in skip (multiple noncontiguous) areas, but only 1/13 (8%) of normal TAs did so. VZV antigen was also found in 12/32 (38%) skeletal muscles adjacent to VZV antigen-positive TAs. Characteristic pathology was seen in 89% of GCA-positive TAs but not in any of the 18 adjacent tissue sections from normal TAs. The relationship between the presence of VZV antigen and the pathologic changes of GCA was statistically significant. Gilden et al. examined far more TA sections than in any previous study, which partly explains their success. When PCR amplification of VZV DNA was carried out on scrapings of VZV antigen-positive TAs, VZV DNA was detected in 18/45 (40%) cases despite the disadvantage of formalin fixation. The presence of VZV in these TAs was also supported by electron microscopy images of herpes virions detected in one of the GCA-positive TA cases. Taken together, these findings are compelling evidence that VZV triggers the immunopathology seen in patients with GCA.

This study was both thorough and rigorous and the authors took care to include appropriate TA controls. However, 3 critical issues arise from these findings, relating to the diagnosis, cause, and therapy of temporal arteritis.

First, at least 50 sections per TA were examined, whereas most hospital pathology laboratories examine only a few sections. The authors suggest that the immunostaining for VZV include at least 10 sections, and preferably even more. This certainly seems reasonable and could now be implemented where feasible, although the question needs to be asked as to how on a national level these additional laboratory assays will be resourced both in terms of the added time and funds needed.

Second, is it possible to be completely certain about a cause and effect relationship between VZV and GCA? The authors' view is that VZV likely triggers the immunopathology seen in patients with GCA, but could VZV reactivation and productive infection merely be a result of inflammation itself reactivating VZV? While it is not possible to be completely certain about causality at this time, the authors provide persuasive and convincing arguments to suggest a causal relation rather than a secondary epiphenomenon. Particularly compelling are

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From Glasgow University Department of Neurology (P.G.E.K.), College of Medicine, Veterinary and Life Sciences, Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland, UK; and the Departments of Microbiology & Immunology and Neurology (H.L.L.), University of Illinois at Chicago.

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their points that the pathology and distribution of VZV antigen in GCA-positive TA is essentially identical to that seen in patients dying of intracerebral VZV vasculopathy; VZV was detected in 74% of TAs confirmed pathologically as GCA; VZV virions were detected in GCA-positive TAs; and the presence of VZV antigen was clearly associated with GCA pathologic changes.

Third, what are the implications for treatment of GCA? Both proven and highly suspected GCA cases are now treated urgently with corticosteroids, which then are continued for months to years to suppress inflammatory activity and the potential serious neurologic complications. The Gilden et al. study indicates that consideration should be given to treating patients with GCA with both corticosteroids and IV acyclovir on the basis that the disease is essentially a VZV vasculopathy. Such treatment is now recommended for intracerebral VZV vasculopathy. The authors also speculate that one possible explanation for the existence of corticosteroid-refractory cases of GCA may be the long-term potentiation of VZV infection by corticosteroid treatment. Despite the important findings described in this seminal article, the combined administration of acyclovir and corticosteroids in patients with GCA seems premature. However, that situation will likely change if a future clinical trial of combined antiviral and corticosteroid therapy in GCA produces substantial benefit compared to patients receiving corticosteroids alone.

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