VZV is the cause of Giant Cell Arteritis - Pro

Joseph R. Berger, M.D., FACP, FAAN, FANA
Professor of Neurology
Perelman School of Medicine
University of Pennsylvania
Extraordinary claims require extraordinary evidence.
VZV Detected in Cranial Nerve and Autonomic Ganglia Sites of Reactivation

- VZV
VZV well recognized cause of both large and small vessel vasculitis with stroke
Well-established Viral Etiologies of Vasculitis

- Polyarteritis nodosa – hepatitis B (HBV)
  - 3 forms of PAN
    - idiopathic generalized PAN
    - cutaneous PAN
    - hepatitis B virus associated PAN
  - 36% of PAN was HBV-PAN until development of the HBV vaccine; now 3%
  - Treatment of HBV-PAN is centered on antiviral therapy

- Cryoglobulinemic vasculitis – hepatitis C (HCV)
  - 90% of patients with mixed cryoglobulinemia have HVC Abs or HCV detected by PCR
  - In patients with HCV-cryoglobulinemic vasculitis, antivirals must be administered with rituximab to achieve complete or partial remission
Giant Cell Arteritis

- Synonyms: Temporal arteritis; Horton’s arteritis
- Most common form of immune-mediated vasculitis in people > 50 yrs
  - Mean age is 70 yr
  - W:M = 2:1
- Characterized by granulomatous inflammation of medium and large vessels
- Classical manifestations include headache, PMR, fever, visual symptoms, fatigue, tender STA; weight loss; jaw claudication; tongue claudication
- ESR > 100 mm/hr common
- Temporal artery biopsy for diagnosis
Mechanisms by which pathogens can elicit autoimmunity

• Molecular mimicry: cross-reactivity between pathogen derived and self derived epitopes
• Epitope spreading: development of immune responses to endogenous epitopes secondary to release of self antigens
• Bystander activation: non-specific activation of autoimmune cells by an inflammatory environment
• Immune response to crypto-antigens: subdominant epitopes normally hidden from T cell recognition
Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis

ABSTRACT

Objective: Varicella-zoster virus (VZV) infection may trigger the inflammatory cascade that characterizes giant cell arteritis (GCA).

Methods: Formalin-fixed, paraffin-embedded GCA-positive temporal artery (TA) biopsies (50 sections/TA) including adjacent skeletal muscle and normal TAs obtained postmortem from subjects >50 years of age were examined by immunohistochemistry for presence and distribution of VZV antigen and by ultrastructural examination for virions. Adjacent regions were examined by hematoxylin & eosin staining. VZV antigen-positive slides were analyzed by PCR for VZV DNA.

Results: VZV antigen was found in 61/82 (74%) GCA-positive TAs compared with 1/13 (8%) normal TAs (p < 0.0001, relative risk 9.67, 95% confidence interval 1.46, 63.69). Most GCA-positive TAs contained viral antigen in skip areas. VZV antigen was present mostly in adventitia, followed by media and intima. VZV antigen was found in 12/32 (38%) skeletal muscles adjacent to VZV antigen-positive TAs. Despite formalin fixation, VZV DNA was detected in 18/45 (40%) GCA-positive VZV antigen-positive TAs, in 6/10 (60%) VZV antigen-positive skeletal muscles, and in one VZV antigen-positive normal TA. Varicella-zoster virus were found in a GCA-positive TA. In sections adjacent to those containing VZV, GCA pathology was seen in 89% of GCA-positive TAs but in none of 18 adjacent sections from normal TAs.

Conclusions: Most GCA-positive TAs contained VZV in skip areas that correlated with adjacent GCA pathology, supporting the hypothesis that VZV triggers GCA immunopathology. Antiviral treatment may confer additional benefit to patients with GCA treated with corticosteroids, although the optimal antiviral regimen remains to be determined. Neurology® 2015;84:1948-1955
Figure 2: Immunofluorescent staining and ultrastructural imaging of VZV-infected temporal artery

A giant cell arteritis-positive temporal artery (A) was examined for the presence of varicella-zoster virus (VZV) antigen in the adventitia (A), media (M), and intima (I). Immunohistochemical staining with rabbit anti-VZV E/D antibody revealed VZV antigen in the media (B, pink color), but not after staining with rabbit anti-herpes simplex virus 1 antibody (C). Immunofluorescent staining with a different mouse anti-VZV Igo antibody than that used for immunohistochemistry in figure 1 revealed VZV antigen in the adventitia (D, red color), but not when primary antibody was omitted (E). Sections adjacent to those containing VZV antigen were prepared for transmission electron microscopy (TEM) and scanning electron microscopy (SEM) as described in the Methods. TEM revealed an enveloped virus particle (F, arrow), and SEM showed a cluster of virus particles in the adventitia (G, arrows). Viral particles appear slightly larger than 200 nm because they were sputter coated with a gold alloy. In panels F and G, scale bars = 300 nm. EM = electron microscopy.
Varicella Zoster Virus Infection in Granulomatous Arteritis of the Aorta

Don Gilden, Teresa White, Philip J. Boyer, Kristin M. Galetto, E. Tessa Hedley-Whyte, Meredith Frank, Dawn Holmes, and Maria A. Nagel

Granulomatous arteritis characterizes the pathology of giant cell arteritis, granulomatous aortitis, and intracerebral varicella zoster virus (VZV) vasculopathy. Because intracerebral VZV vasculopathy and giant cell arteritis are strongly associated with productive VZV infection in cerebral and temporal arteries, respectively, we evaluated human aortas for VZV antigen and VZV DNA. Using 3 different anti-VZV antibodies, we identified VZV antigen in 11 of 11 aortas with pathologically verified granulomatous arteritis, in 1 of 1 cases of nongranulomatous arteritis, and in 5 of 18 control aortas (28%) obtained at autopsy. The presence of VZV antigen in granulomatous aortitis was highly significant ($P = .0001$) as compared to control aortas, in which VZV antigen was never associated with pathology, indicating subclinical reactivation. VZV DNA was found in most aortas containing VZV antigen. The frequent clinical, radiological, and pathological aortic involvement in patients with giant cell arteritis correlates with the significant detection of VZV in granulomatous aortitis.

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Varicella Zoster Virus Ischemic Optic Neuropathy and Subclinical Temporal Artery Involvement

Richard Salazar, MD; Andrew N. Russman, DO; Maria A. Nagel, MD; Randall J. Cohrs, PhD; Ravi Mahalingam, PhD; D. Scott Schmid, PhD; Bette K. Kleinschmidt-DeMasters, MD; Eve M. VanEgmond, MD; Don Gilden, MD

**Objective:** To demonstrate varicella zoster virus (VZV) infection in an asymptomatic extracranial (temporal) artery in a patient with ischemic optic neuropathy produced by VZV vasculopathy in whom the pathological changes were mistakenly identified as giant cell arteritis.

**Design:** Case report.

**Setting:** Teaching hospital, pathology and virology laboratory.

**Patient:** An 80-year-old man with left ophthalmic distribution zoster who developed left ischemic optic neuropathy.

**Intervention:** An ipsilateral temporal artery biopsy revealed inflammation that was mistakenly identified as giant cell arteritis. The patient was initially treated with steroids but his condition did not improve. When the diagnosis of VZV vasculopathy was confirmed virologically and the patient was treated with intravenous acyclovir, his vision improved.

**Results:** Pathological and virological studies provided proof of VZV vasculopathy in the asymptomatic temporal artery. Varicella zoster virus antigen was abundant in arterial adventitia and scattered throughout the media. With intravenous antiviral therapy, the patient’s vision improved.

**Conclusion:** Although in previously studied patients who died of chronic VZV vasculopathy after 10 to 12 months, VZV antigen was present exclusively in the intima, collective analyses of chronic cases and the asymptomatic VZV-infected temporal artery suggest that virus enters arteries through the adventitia and spreads transmurally to the intima.

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Headaches due to giant cell arteritis following herpes zoster ophthalmicus in an elderly patient

Case report

An 80-year-old woman presented to the out-patient neurology clinic complaining of right upper facial pain in the distribution of the first division of the trigeminal nerve (V1), right eye photophobia, and a right-sided headache. The patient had been diagnosed at an outside clinic 2 months prior to presentation to our clinic with HZO after developing a painful vesicular rash in the right V1 distribution along with corneal involvement without visual compromise. She was treated with an appropriate course of oral valacyclovir and an ophthalmic prednisone suspension.

The vesicular rash improved, but the patient was left with neuropathic pain in the V1 distribution and persistent photophobia consistent with PHN. A new right-sided headache began 4–6 weeks after the onset of HZO. She described this as being distinct from the neuropathic pain. This new pain was located in the right tempo-parietal area and was described as a dull constant ache over the entire area. There was also associated scalp tenderness without any scalp nodules or necrotic areas appreciated. Temporal artery pulsations were normal and the arteries appeared to be normal in consistency. She denied any visual loss or distortions and the vision examination was normal. She did not have symptoms suggestive of polymyalgia rheumatica.
Herpes Zoster as a Risk Factor for Incident Giant Cell Arteritis

Bryant R. England,1 Ted R. Mikuls,1 Fenglong Xie,2 Shuo Yang,2 Lang Chen,2 and Jeffrey R. Curtis2

Objective. Histopathologic studies have implicated herpes zoster (HZ) as a causative organism of giant cell arteritis (GCA). The purpose of this study was to assess the epidemiologic association of HZ events with incident GCA.

Methods. We performed a retrospective cohort study in 2 large independent US administrative data sets: Medicare 5% and Truven Health Analytics MarketScan. Eligible subjects had 12 months of continuous coverage, were >50 years old, and had no history of GCA or polymyalgia rheumatica. HZ events (complicated and uncomplicated) and GCA were identified by the presence of International Classification of Diseases, Ninth Revision, Clinical Modification codes from physician visit or hospital discharge records. Antiviral therapies and vaccinations were identified from prescription claims and drug codes. Risk of incident GCA was calculated using multivariable Cox proportional hazards regression.

Results. Among 16,686,345 subjects, a total of 5,942 GCA cases occurred, with 3.1% (MarketScan) and 6.0% (Medicare) having preceding HZ events. Unadjusted GCA incidence rates were highest in the groups with complicated and uncomplicated HZ. After multivariable adjustment, complicated HZ was associated with an increased risk of GCA (hazard ratio [HR] 1.99 [95% confidence interval (95% CI) 1.32–3.02] in the Medicare cohort and 2.16 [95% CI 1.46–3.18] in the MarketScan cohort), as was uncomplicated HZ (HR 1.42 [95% CI 1.02–1.99] and HR 1.45 [95% CI 1.05–2.01] in the respective cohorts). Vaccination and antiviral treatment were not consistently associated with GCA risk, although antiviral treatment was marginally associated with a decreased risk of GCA in the Medicare cohort (HR 0.67 [95% CI 0.46–0.99]).

Conclusion. HZ is associated with an increased risk of GCA. The infrequency of HZ in GCA patients suggests that it is only one potential trigger for GCA. Antivirals and vaccination did not consistently mitigate this risk.
74 year old woman with 7 days of pain on right side of head, shooting pain in right ear, and blurred vision in right eye

- Pain worsened with chewing and sleeping on side
- Right temporal artery palpable but not tender or inflamed
- ESR 53 mm/h and CRP 0.4
- Admitted for IVMP and B TA biopsies
- Small vessel vasculitis in the adventitia with perineural lymphocytic aggregation
- 4 hours after procedure outbreak of vesicular rash
- Although this case was attributed to VZV arteritis there is an overlap between VZV vasculitis and GCA vasculitis
  - Lesion is often transmural often with necrosis
  - Granulomas may be seen in both
  - Multinucleate giant cells and epithelioid macrophages in both
Varicella zoster virus triggers the immunopathology of giant cell arteritis

Don Gilden and Maria A. Nagel

Summary
The presence of VZV in Bx-positive and Bx-negative GCA temporal arteries indicates that VZV triggers the immunopathology of GCA. However, the presence of VZV in about 20% of temporal artery biopsies from non-GCA postmortem controls also suggests that VZV alone is not sufficient to produce disease. Treatment trials should be performed to determine if antiviral agents confer additional benefits to corticosteroids in both Bx-positive and Bx-negative GCA patients. These studies should also examine whether oral antiviral agents and corticosteroids are as effective as intravenous acyclovir and corticosteroids. Appropriate dosage and duration of treatment also remain to be determined.