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Short communication

Biopsy-negative, varicella zoster virus (VZV)-positive giant cell arteritis, zoster, VZV encephalitis and ischemic optic neuropathy, all in one

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ABSTRACT

A 72-year-old man developed clinical features of giant cell arteritis (GCA) and ipsilateral ophthalmic-distribution zoster, followed within 2 weeks by VZV encephalitis and 2 months later by ischemic optic neuropathy. Temporal artery biopsy was histopathologically negative for GCA, but contained VZV antigen and VZV DNA in multiple non-contiguous (skip) areas. The collective clinical and laboratory findings revealed a remarkably close temporal association of zoster, multifocal VZV vasculopathy with temporal artery infection, biopsy-negative VZV-positive GCA and VZV encephalitis.

1. Introduction

Within a 2-month period, a 72-year-old man developed clinical features of giant cell arteritis (GCA), ipsilateral ophthalmic-distribution zoster, encephalitis and ischemic optic neuropathy. Because VZV has been closely associated with each of these neurological conditions, the temporal artery and CSF were examined for the presence of VZV antigen and VZV DNA.

2. Case report

An immunocompetent 72-year-old-man presented with a 1-week history of left-sided fronto-temporal head pain (both superficial and deep), anorexia, nausea and weight loss. He denied jaw claudication and muscle aches. Scalp was tender to palpation (left > right), but temporal artery (TA) pulses were normal. Erythrocyte sedimentation rate (ESR) was 36 mm (normal < 30) and C-reactive protein (CRP) was 0.6 mg/dL (normal < 0.5). Doppler ultrasound (DU) detected a halo sign, indicating inflammation in both TAs (right > left) (Fig. 1A). On day 7, the patient was treated for presumptive GCA with intravenous methylprednisolone (60 mg once) followed by oral prednisolone (80 mg/day). After 4 h, he developed left ophthalmic-distribution zoster with keratitis and was treated with valacyclovir (1 g tid). Eleven days later, head pain lessened, but he became apathetic and disoriented, with memory deficit and incoherent speech. On day 21 (14 days after corticosteroid treatment), because the halo sign was greater on the right, a right TA biopsy was performed; examination of 4 sections showed only mild intimal hyperplasia. On day 22, ESR, CRP and brain MRI were normal. CSF contained 29 cells/mm^3, predominantly mononuclear, CSF protein was 114 mg/dL and glucose was 228 mg/dL; PCR amplified 9.91×10^2 copies VZV DNA per mL CSF. DU indicated regression of inflammation (Fig. 1B). Corticosteroids were tapered and antiviral treatment was switched from oral valacyclovir to intravenous acyclovir (750 mg tid for 3 weeks). Encephalitis resolved, although one week after corticosteroid withdrawal (2 months after initial presentation), headache and scalp tenderness recurred, accompanied by left eye vision "clouding", myalgia and asthenia. Fundus exam revealed a pale left disk, and optical coherence tomography revealed left superior temporal

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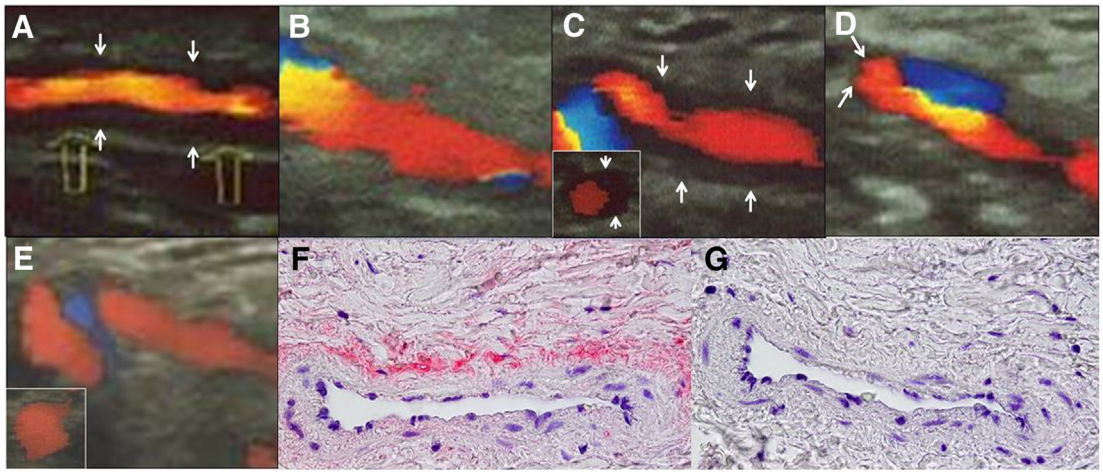

Fig. 1. Examination of the temporal artery by Doppler ultrasound and by immunohistochemistry. (A) Right temporal artery (TA) Doppler ultrasound (DU) reveals a "halo sign", the black hypoechoic area denoted by arrows around the perfused lumen of the TA due to inflammation of the vessel wall in patients with giant cell arteritis (GCA). (B) Disappearance of the halo sign 2 weeks after treatment with corticosteroids and valacyclovir. (C) Reappearance of the halo sign (arrows) 3 weeks after discontinuing corticosteroids. Inset shows the temporal artery in a transverse plane. (D) DU reveals occlusion of the temporal artery (arrows). (E) After resuming corticosteroids for presumptive GCA, serial DUs showed resolution of the halo sign; inset shows the temporal artery in a transverse plane. Of 150 5-μm sections cut from the formalin-fixed, paraffin-embedded TA biopsy, every 3rd section was immunostained with antibody to VZV as described [8]. Eight nonconsecutive sections (skip areas) revealed VZV antigen in the arterial adventitia (pink color) (F) that was not seen with pre-immune serum from the same rabbit (G).

quadrant atrophy consistent with posterior ischemic optic neuropathy (ION). ESR and CRP increased to 98 mm and 13.7 mg/dL, respectively, and hemoglobin dropped from 15.0 g/dL to 12.1 g/dL. Repeat DU revealed a renewed halo sign (Fig. 1C) and right temporal artery occlusion (Fig. 1D). Despite the GCA-negative biopsy, retreatment with oral prednisolone (60 mg/day) led to rapid sustained clinical improvement and normalization of lab parameters and TA DU (Fig. 1E). After 1.5 years, corticosteroids had been tapered and the patient was treated with methotrexate for presumptive corticosteroid myopathy. He is stable on oral methotrexate (15 mg/week). Virological examination of the TA biopsy revealed VZV antigen (Fig. 1F). In addition, 5 VZV-positive sections were scraped with a scalpel and pooled, placed into 200 ul lysis buffer with proteinase K (DNeasy Blood and Tissue Kit; Germantown, MD), followed by DNA extraction per the manufacturer's protocol. Using Applied Biosystem's 7500 software v2.0.6, real-time PCR was performed to detect cellular (GAPdH) DNA along with serial dilutions of VZV DNA. The viral Cq value of the TA sample was determined by comparing it to the lowest level of amplification to VZV DNA standards. A Cq value of 32.8 was obtained for GAPdH and 33.6 for VZV DNA, revealing that the sample contained both cell DNA and VZV DNA.

3. Discussion

The most remarkable and instructive feature of this novel case is the near simultaneous development of clinical features of GCA followed by ipsilateral ophthalmic-distribution zoster, VZV encephalitis and ION. The diagnosis of biopsy-negative GCA was based on our patient's clinical presentation, his increasing and eventually marked elevation of sedimentation rate and CRP, and favorable clinical response to corticosteroids, including improvement of the halo sign after treatment of each episode.

While no independent criteria validate the presence of GCA when a TA biopsy is negative, the American College of Rheumatology lists 5 criteria for classification of GCA that assist in diagnosis, with the caveat that these are not diagnostic and serve mainly to differentiate GCA from other types of vasculitis [1]. The criteria are: (1) age of onset ≥ 50 years, (2) new severe headache, (3) temporal artery abnormality such as tenderness to palpation or decreased pulsation, (4) ESR ≥ 50 mm/h and (5) abnormal TA biopsy showing vasculitis with mononuclear cell or granulomatous inflammation, usually with giant cells. The presence of at least 3 of these 5 criteria yields a sensitivity of 93% and a specificity of 91% compared to patients with other vasculitides. Our patient satisfied each of the first 4 criteria; in addition, both pain and the halo sign resolved with corticosteroids. For decades, pathologists have recognized that TA biopsies are normal in 10–30% of patients with suspected GCA [2,3], most likely due to the segmental nature of GCA and also reflecting the number of sections examined. In fact, only 4 sections of the TA from our patient were examined histopathologically.

The onset of biopsy-negative GCA and zoster within one week and the presence of VZV in 8 skip areas of the TA strongly suggest a role for VZV in producing GCA. Recent reports have revealed a striking association between VZV and TA infections, including: a case of multifocal VZV vasculopathy manifested by ION and TA infection that developed one month after ipsilateral ophthalmic-distribution zoster [4]; 2 additional cases of multifocal VZV vasculopathy manifested by ION and TA infection with no history of zoster [5,6]; and the detection of VZV antigen and DNA in archived material from 5 subjects, all of whom had ION, in analysis of 24 GCA-negative TAs [7], indicating that VZV multifocal vasculopathy can present with the full spectrum of clinical features and laboratory abnormalities seen in GCA and suggesting that VZV might actually cause GCA. More compelling evidence linking VZV to GCA came from analysis of a TA that was GCA-negative pathologically, but contained multiple skip areas with VZV antigen; additional pathological analysis of sections adjacent to those containing VZV antigen revealed the classic pathological changes of GCA [8].

Our case represents the closest temporal association of biopsy-negative GCA with VZV antigen and VZV DNA in the TA followed by zoster, VZV encephalitis and ION. While a favorable response to corticosteroids has long been recognized in patients with GCA as well as biopsy-negative GCA, further studies are needed to determine whether antiviral treatment of GCA confers additional benefit.

Conflict of interest statement

All authors report no conflicts of interest.

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