Anti-neutrophil cytoplasmic antibody–associated vasculitis associated with infectious mononucleosis due to primary Epstein–Barr virus infection: report of three cases

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Abstract

Although the aetiology of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis remains unclear, it is generally believed that environmental factors such as infections contribute to its development of ANCA-associated vasculitis. Prior Epstein–Barr virus (EBV) infection is reported to be a trigger of systemic vasculitis. We herein report three cases of ANCA-associated vasculitis presenting with infectious mononucleosis due to primary EBV infection. The causal link between the two pathologies could not be proved, but primary EBV infection may play a role in the initiation or exacerbation of ANCA-associated vasculitis. Future studies are necessary to determine the interaction between these diseases conditions.

Keywords: anti-neutrophil cytoplasmic antibody; Epstein–Barr virus; infectious mononucleosis; vasculitis

Background

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis includes granulomatosis with polyangiitis (Wegener’s granulomatosis) and microscopic polyangiitis. It is postulated that autoimmunity and infectious mechanisms play a role in the pathogenesis [1]. The presence of infection suggests that pathogens may act as potential triggers of an inflammatory cascade leading to vascular inflammation. We report here three cases of ANCA-associated vasculitis that presented with infectious mononucleosis due to primary Epstein–Barr virus (EBV) infection. Although a causal link between the two pathologies could not be proved, the present cases indicate that primary EBV infection contributes to the initiation or exacerbation of ANCA-associated vasculitis.

Case 1

A previously healthy 15-year-old Japanese woman presented at our hospital with a 1-month history of sore throat, purulent nasal discharge, high fever and general fatigue. She had small spot of purpura on her right elbow (Supplementary Figure S1A), bilateral reddish and swollen tonsils coated with white fur and bilateral lymphadenopathy in the neck. Laboratory data revealed an elevated white blood cell (WBC) count, C-reactive protein (CRP) and proteinase 3 (PR3)–ANCA titre. Urinalysis showed proteinuria, spot urine protein-to-creatinine ratio of 1.0, gross haematuria with dysmorphic red blood cells (RBC) and RBC casts. IgM/IgG antibodies to EBV viral capsid antigen (VCA) and EBV nuclear antigen (EBNA) were positive (Tables 1 and 2). Chest computed tomography (CT) showed bilateral lung inﬁltrates and patchy ground glass opacity. Bronchoscopy revealed alveolar haemorrhage. Skin biopsy of the purpura on her right elbow revealed panendothelial leucocytoclastic vasculitis with fibrinoid degeneration, but no granuloma (Supplementary Figure S1B–D). Renal biopsy demonstrated a pauci-immune necrotizing glomerulonephritis with cellular crescents in more than 50% of the glomeruli (Supplementary Figure S1E). Nasal biopsy revealed necrotizing vasculitis with severe inflammation and granulomatous inflammation (Supplementary Figure S1F and G). No specific bacteria were detected in her sputum, ear discharge, urine or blood cultures. Based on these findings, she was diagnosed as having granulomatosis with polyangiitis, probably triggered by primary EBV infection. Follow-up data taken 3 months later are consistent with primary EBV infection (Table 2). Methylprednisolone pulse therapy and intravenous cyclophosphamide induced remission, and she has since been in remission for 10 months with azathioprine and low-dose prednisolone.

Case 2

An 80-year-old Japanese woman with 2-year diagnosis of nontuberculous mycobacterial infections (Mycobacterium
avium-intracellularare) had been suffering from hearing loss for 2 months before admission, and had been diagnosed as having otitis media by an otolaryngologist. Antibiotics had been ineffective. One month before admission, fever and appetite loss developed. On admission, she had high fever, general fatigue and hearing loss due to bilateral otitis media. Neither enlarged tonsils nor cervical lymphadenopathy were noted. Laboratory data revealed an elevated WBC count, CRP and myeloperoxidase (MPO)-ANCA titre levels. Urinalysis showed proteinuria with a spot urine protein-to-creatinine ratio of 1.0, gross haematuria with dysmorphic RBC and RBC casts. IgM/IgG antibodies to EBV VCA and EBNA were positive (Tables 1 and 2). Chest CT showed small nodules and bronchiectasis, but no abnormal findings were detected. No specific bacteria were detected in sputum, ear discharge, urine or blood cultures. Follow-up data taken 2 months later indicated the presence of primary EBV infection (Table 2). Based on these results, she was diagnosed as having microscopic polyangiitis related to primary EBV infection. Methylprednisolone pulse therapy induced remission, and she has since been in remission for 5 months with mizoribine and low-dose prednisolone.

Case 3
A 57-year-old Japanese man had experienced fever, cough without haemoptysis, appetite loss and skin rashes for 2 weeks before admission. He was diagnosed as having scleritis by an ophthalmologist 1 year previously, which was unresponsive to glucocorticoid eye drops. On admission, he had high fever and general fatigue. He had purpura on the lower extremities and ulcers of the tongue (Supplementary Figure S3A and B). Neither enlarged tonsils nor cervical lymphadenopathy were observed. Laboratory data revealed elevated CRP and MPO-ANCA titre levels. Urinalysis showed proteinuria with a spot urine protein-to-creatinine ratio of 0.5, gross haematuria with dysmorphic RBC and RBC casts. IgM/IgG antibodies to EBV VCA and EBNA were positive (Tables 1 and 2). Chest CT demonstrated patchy consolidation and air bronchograms in right lung fields. Bronchoscopy revealed alveolar haemorrhage. Skin biopsy showed leucocytoclastic angiitis but no granuloma (Supplementary Figure S3C). Tongue biopsy revealed findings of severe granulomatous inflammation (Supplementary Figure S3D). Renal biopsy was undertaken but no abnormal findings were detected. No specific bacteria were detected in sputum, ear discharge, urine or blood cultures. Follow-up data taken 2 months later are consistent with primary EBV infection (Table 2). Based on these results, he was diagnosed with granulomatosis with polyangiitis, probably exacerbated by primary EBV infection. Methylprednisolone pulse therapy and intravenous cyclophosphamide-induced remission, and he has since been in remission for 3 months with methotrexate and low-dose prednisolone.

Discussion
We herein report three cases of ANCA-associated vasculitis associated with infectious mononucleosis due to primary EBV infection. Our cases were diagnosed as ANCA-associated vasculitis presenting simultaneously with primary EBV infection on their initial visit. The symptoms of ANCA-associated vasculitis at disease onset

Table 1. Profiles of three cases with ANCA-associated vasculitis

| Case | Normal range | Case 1 | Case 2 | Case 3 |
|------|--------------|-------|-------|-------|
| Age (years) | | | | 15 | 80 | 57 |
| Gender | | Female | Female | Male | | |
| WBC (x10^9/L) | | 4.8–9.8 | 16.3 | 10.3 | 7.0 |
| Hgb (g/L) | | 100–140 | 101 | 100 | 102 |
| PLT (x10^9/L) | | 130–320 | 255 | 363 | 409 |
| CRP (mg/L) | | 0.0–3.0 | 141.7 | 82.2 | 110 |
| AST (U/L) | | 5–40 | 78 | 49 | 22 |
| ALT (U/L) | | 5–40 | 82 | 35 | 32 |
| Cr (µmol/L) | | 82.7 | 88.4 | 106.1 | |
| MPO-ANCA (<20) | | <10 | 324 | <10 | |
| PR3-ANCA (<10) | | 101 | <10 | <10 | <10 |
| Anti-GBM antibodies (EIA) (<10) | | <10 | <10 | <10 | <10 |
| CMV VCA IgM (EIA) (<0.5) | | 2.2 | 3.2 | 7.7 | |
| CMV VCA IgG (EIA) (<0.5) | | 2.4 | 2.2 | 7.7 | |
| CMV EBNA (FA) (<10) | | 80 | 80 | 80 | |
| EB VCA IgM (EIA) (<0.5) | | 6.2 | 5.7 | 11.3 | |
| EB VCA IgG (EIA) (<0.5) | | 2.4 | 2.2 | 2.2 | |
| EB DNA (<2.0 x 10^1 copies/10^6 cells) | | 2.0 x 10^3 | 2.0 x 10^3 | 2.0 x 10^3 | |

ANCA, antineutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase 3; GBM, glomerular basement membrane; CMV VCA, cytomegalovirus viral capsid antigen; EIA, enzyme immunoassay.

Table 2. Serologic responses to EB virus infection in the present three cases

| Case | Normal range | Case 1 | Case 2 | Case 3 |
|------|--------------|-------|-------|-------|
| EB VCA IgM (EIA) (<0.5) | | | | | |
| EB VCA IgG (EIA) (<0.5) | | 2.4 | 2.2 | 2.2 | |
| EB DNA (<2.0 x 10^1 copies/10^6 cells) | | 2.0 x 10^3 | 2.0 x 10^3 | 2.0 x 10^3 | |

EB VCA, Epstein–Barr virus viral capsid antigen; EIA, enzyme immunoassay; FA, fluorescent antibody; EBNA, EBV nuclear antigen; EB DNA, EB virus-DNA copy number in the peripheral blood mononuclear cells (copies/10^6 cells) was determined by real-time PCR as described previously [2].
overlap substantially with those due to the infectious processes. A variety of cases involving ANCA and infection have been reported, including ANCA-associated vasculitis following bacterial pulmonary infections, wound infection, fungal infection and *E. coli* pyelonephritis [3–7]. EBV is reportedly linked with various forms of vasculitis, including leucocytoclastic vasculitis, granulomatous vasculitis, Kawasaki disease, polyarteritis nodosa, Duncan disease, systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis [8–15]. A recent case report linked primary EBV infection with ANCA-associated vasculitis, which is similar to this case [16]. Pender suggested a role of EBV in causing autoimmune diseases via interaction between B cells infected by EBV and autoreactive T cells [17]. In addition, ANCA was detected in 6% of patients with infectious mononucleosis and positive sera for IgM antibodies against EBV as an epiphrenomenon in EBV infection [18].

In the present three cases, EBVCA IgM, EBVCA IgG and EB EBNA were detected on admission, which indicates both the possibility for primary infection and reactivation of EBV. However, this pattern of simultaneous detection in immunocompetent individuals is typically interpreted as late primary infection [19]. Therefore, we consider that these cases are primary EBV infection. EBV DNA is frequently detected in whole blood within 14 days of symptom onset in primary infection [20], and viral loads ranged from $3.8 \times 10^3$ to $6.6 \times 10^4$ copies/ml [21]. After the initiation of an immune response, the viral load decreases rapidly in whole blood, and becomes undetectable after 3–4 weeks [22]. In our patients, EB DNA data examined at least 1 month after symptom onset are also compatible with time sequence data for primary EBV infection. Based on clinical settings, we considered the roles of primary EBV infection, but we could not completely rule out the possibilities of EBV reactivation.

In the present cases, we had to consider EBV-associated renal diseases in the differential diagnosis. Lee and Kjellstrand reported acute renal failure to be very uncommon in patients with EBV infection, with a prevalence of ~1.6% [23]. Tubulointerstitial nephritis, sometimes accompanied by mesangial proliferation or focal tubular necrosis, is reported to be the most common pathological finding in EBV-associated acute renal failure [24]. Glomerular abnormalities such as immune-complex-mediated glomerulonephritis, membranous nephropathy and minimal change nephrotic syndrome have been reported, but are considered to be rare [25, 26]. In our cases, there were no findings of tubulointerstitial nephritis or the glomerular diseases described above; thus, renal dysfunction in our cases is not likely to be EBV-associated acute renal failure.

We were concerned about the possibility of progression to chronic active EBV infection during immunosuppressive therapy. Chronic active EBV infection is known to be a serious feature of EBV infection and is characterized by chronic or recurrent infectious mononucleosis-like symptoms, abnormal anti-EBV antibody patterns and increased EBV load in the peripheral blood. However, none of the present cases showed elevation of EBV DNA in peripheral blood mononuclear cells during immunosuppressive therapy (Table 2). Therefore, we did not consider our cases to have progressed to chronic active EBV infection.

In conclusion, these findings suggest that primary EBV infection is involved in the aetiology of onset or exacerbation of ANCA-associated vasculitis, while a firm determination linking the infectious agent to the pathogenesis of vasculitis was not possible. Further studies into the pathogenesis between these diseases are therefore necessary.

### Supplementary data

Supplementary data is available online at [http://ndt.oxfordjournals.org](http://ndt.oxfordjournals.org).

**Conflict of interest statement.** None declared.

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