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Anti-Glomerular Basement Membrane Antibody Associated With Human Parvovirus B19 Infection

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An eleven years old girl developed glomerulonephritis, showing positive antibody against glomerular basement membrane (anti-GBM) associated with acute human parvovirus B19 (HPVB19) infection. She was admitted with fever, rash, and joint pain. Additionally, hematuria, proteinuria, and hypocomplementemia were present. HPVB19 DNA and anti-GBM antibody were positive in blood. A kidney biopsy showed mesangial proliferative glomerulonephritis. Subsequently, steroid pulse therapy was given, followed by oral prednisolone and cyclophosphamide. After the steroid pulse therapy, the urinary findings improved, and anti-GBM antibody became undetectable, also the glomerulonephritis has not recurred. The HPVB19 infection appeared to have induced the production of anti-GBM antibody in this patient.

Key words: anti-glomerular basement membrane (anti-GBM) antibody, human parvovirus B19 (HPVB19) infection, glomerulonephritis

INTRODUCTION

HPVB19 infection is frequently seen in pediatric population, and is characterized by various clinical features, including infectious erythema (1). HPVB19 infection is also considered to cause immunoreactivity in humans, and is correlated with various autoantibodies and autoimmune diseases, such as SLE (1-3). Antibody against glomerular basement membrane (anti-GBM antibody) is an autoantibody that can cause rapidly progressive glomerulonephritis and Go odpasture's syndrome; the prognosis of such patients who develop renal failure or pulmonary hemorrhage is extremely poor (4,5). A previous study reported that the incidence of anti-GBM antibody-positive nephritis increased when HPVB19 infection was prevalent (6), however, to the best of our knowledge, no previous cases with both HPVB19 infection and anti-GBM antibody verified serologically have been reported.

We present a case of an 11-year-old girl with glomerulonephritis and production of anti-GBM antibody, following HPVB19 infection.

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CASE PRESENTATION

A 11-year-old Japanese girl was admitted to our hospital, because of fever, rash, and hepatic dysfunction. She and her family had no past history of renal disease or collagen diseases. Two weeks before admission, she visited her family physician due to fever, headache, and nausea. In the morning of the day before admission, skin rash appeared on her extremities. Her physician pointed hepatic dysfunction with blood testing, and she was referred to our hospital. On admission, her body temperature was 38.3℃, blood pressure was 107/79 mmHg. Skin rash accompanied by a sense of burn was present on the forearms and lower thighs. Redness of throat and tonsillar swelling, as well as cervical lymph node enlargement, were noted. No abnormalities were seen in the thorax or abdomen.

Laboratory findings: mildly elevated liver enzymes in blood (AST: 97 IU/l, ALT: 133 IU/l and LDH: 305 IU/l), hypocomplementemia (C3: 85mg/dl, C4: 13 mg/dl and CH50: 23.2 mg/dl), and CRP (0.2 mg/dl) serum IgG (1070 mg/dL), IgA (261 mg/dL), IgM (282 mg/dL) were in normal range. No abnormalities in the electrolytes, coagulation, or renal function (blood urea nitrogen: 7.9 mg/dl and serum creatinine: 0.51 mg/dl and creatinine clearance 119

mL/min per 1.73 m^2) were noted. Urinalysis: proteinuria (2+) and hematuria (3+) were observed; microscopic examination of the urinary sediments revealed the presence of red blood cell casts. Plain chest X-ray, and computed tomography examination, and abdominal US did not show any abnormalities.

Special tests: Anti-nuclear antibody was negative, and anti-streptolysin O (ASO) titers were not elevated; myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA), <10 EU; proteinase-3 (PR-3)-ANCA, <10 EU, whereas markedly increased anti-GBM antibody, 79 EU (ELISA, normal range, <10 EU) were found. Both IgM and IgG antibody titers against HPVB19 determined by enzyme immunoassay, were positive, and DNA of HPVB19 was also detected in plasma by polymerase chain reaction. While viral antibodies against hepatitis B and C, Epstein-Barr virus, cytomegalovirus, rubella, were all negative.

Since anti-GBM antibody was positive, a renal biopsy was performed on day 16 of the illness, in order to rule out rapidly progressive glomerulonephritis. On Light microscopy, 20 glomeruli were identified, and 70% of the glomeruli adhered to Bowman's capsule. Diffuse proliferation of the substrate and of mesangial cells was observed. There was no crescent formation; there were no findings indicative of interstitial inflammatory cell infiltration or vasculitis. Immunostaining showed granular deposition of IgA, IgM, C3, and fibrinogen in the mesangium. Linear deposition of IgG, which is a characteristic feature of anti-glomerular basement membrane antibody-positive nephritis, was absent. Electronmicroscopy showed many dense deposits under the endothelium of the loop near the mesangium, whereas no dense deposits were seen inside the basal membrane or under the epithelium. Hence, the diagnosis of mesangial proliferative glomerulonephritis was made based on those pathologic findings.

Clinical course after admission (Fig.1): After admission, given that the findings were thought to be transient symptoms caused by a viral infection, the patient was monitored and received fluid infusion, and the hepatic enzyme levels gradually improved. However, fever and rash recurred, and the patient developed joint pain, urinary findings did not improve. On the 10th day after admission, methylprednisolone pulse therapy (which consisted of 3 consecutive days of 900 mg per day) was given, followed by oral prednisolone and cyclophosphamide. After steroid pulse therapy, the urinary findings improved. Eventually, the antiglomerular basement membrane antibody titer normalized, and the patient was discharged 33 days after admission. Cyclophosphamide was given for 8 weeks, and prednisolone was for 6 months with appropriate dose reductions.

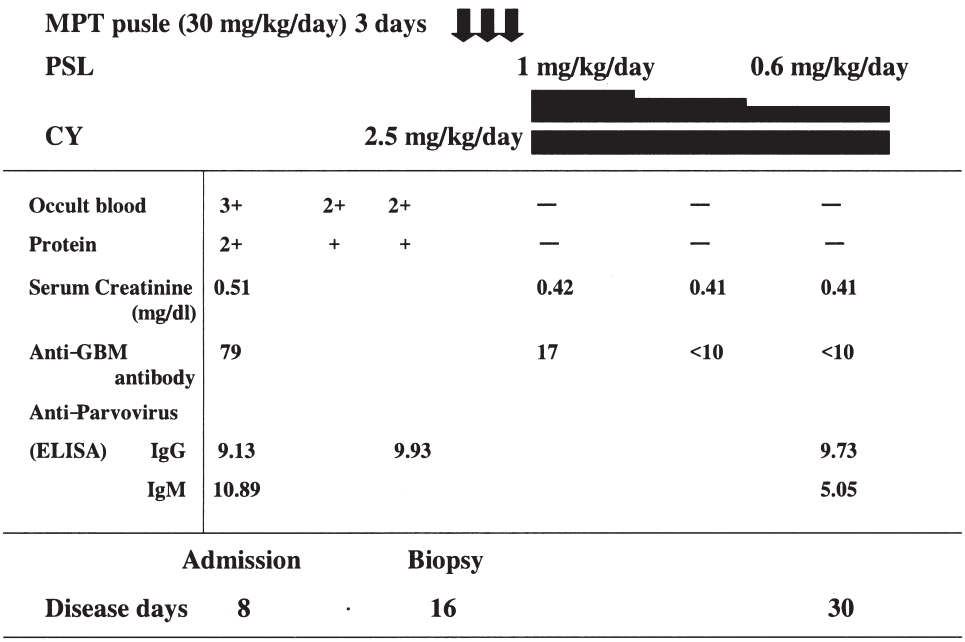

Fig. 1. Clinical course after admission. Abbreviation: MPT, methylprednisolone; PSL, prednisolone; CY, cyclophosphamide. ELISA, Enzyme-linked immunosorbent assay.

DISCUSSION

Parvovirus B19 infection is common in childhood. In general, the infection causes only mild cold-like symptoms; it may rarely cause severe complications (1). Recent studies have documented parvovirus-induced nephropathy that can occur in the absence of underlying disease (7,8).

It has been considered that viral infection occasionally damages kidney, and that damage can occur in two ways: i) viruses directly induce nephropathy; and ii) immune complexes cause nephropathy (9). Based on pathological examination, HPVB19 is believed to cause nephropathy in two ways: direct viral invasion, which damages vascular endothelial cells with thrombotic microangiopathy on pathology (10); and the production of immune complexes, whose deposition can induce nephropathy resulting in mesangial proliferative glomerulonephritis (8). In our case, blood tests on admission confirmed hypocomplementemia, and a kidney biopsy showed mesangial proliferative glomerulonephritis. Immunostaining and electron-microscopy showed deposition of IgA, IgM, and C3 in the mesangium, as well as dense deposits in mesangial cells and below the endothelium. These findings are consistent with those of previous reports of HPVB19-induced glomerulonephritis.

HPVB19 binds with its receptor, P antigen in human body (11). The P antigen is known to exist in erythroblastic cells, megakaryocytes, and vascular endothelial cells (12). When these cells are damaged with HPVB19 infection, symptoms, such as anemia and thrombocytopenia, occur. Furthermore, when vascular endothelial cells are damaged, vasculitis, such as hemolytic uremic syndrome and vascular purpura, may occur (8-13).

HPVB19 infection can cause human immunoreactivity. Chou *et al* (2) reported a patient in whom HPVB19 induced the production of anti-neutrophil cytoplasmic antibody (ANCA) and anticardiolipin antibody (aCL). HPVB19 infection can induce the production of various autoantibodies that causes symptoms like autoimmune diseases (1-3). Claudio *et al* (14) reported that anti-HPVB19 antibody detected in patients who developed autoimmune disease-like symptoms following HPVB19 infection exhibited affinity towards human keratin, type II collagen, ssDNA, and cardiolipin. This suggests that HPVB19 infection can potentially induces an autoimmune state in various organs.

In our case, a marked increase in anti-GBM antibody titer was also detected. Anti-GBM antibody is an autoantibody against type IV collagen, which is located in the basal membrane. This autoantibody is thought to cause Goodpasture's syndrome and rapidly progressive glomerulonephritis. In many cases, renal function decreases rapidly and is accompanied by lethal pulmonary bleeding (5). However, it is not clear whether renal function was ever compromised by anti-GBM antibody, and it may not represent pathogenic antibodies in our case. To confirm the binding specificity, a Western blot may be necessary using human GBM or collagen. In our case, however, the amount of the patient's renal sample was too small to confirm the specificity.

Although the mechanism of antiglomerular basement membrane antibody production is still unknown enough, the involvement of viral infection has been previously reported (15). Williams *et al* (6) reported that the incidence of anti-GBM antibody-positive nephritis was increased when the outbreak of HPVB19 infection was occured. Their report was not based on a serological approach. To our knowledge, no previous cases with HPVB19 and anti-GBM antibody verified serologically have been reported. The mechanism for the production of anti-GBM antibody followed by HPVB19 infection was not be clarified. But we may propose a hypothesis that HPVB19 infection damages vascular endothelial cells and induces an immunoreaction to type IV collagen located in the basal membrane. This would result in the production of anti-GBM antibody.

Generally, virus-induced rash, hepatopathy, and nephropathy are transient, and have favorable outcomes. However, as in the present case, it should be noted that a viral infection such as HPVB19 can occasionally cause autoimmune disease such as anti-GBM antibody-positive nephritis and acute renal failure.

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