Anti-neutrophil Cytoplasmic Antibody (ANCA)-associated Vasculitis Associated with Primary Biliary Cirrhosis: A Case Report and Literature Review

Hiroyuki Yamashita, Akitake Suzuki, Yuko Takahashi, Hiroshi Kaneko, Toshikazu Kano and Akio Mimori

Abstract

We herein report a rare case of microscopic polyangiitis with primary biliary cirrhosis (PBC) and a literature review of six previously reported cases of PBC complicated by anti-neutrophil cytoplasmic antibody-associated vasculitis. Due to the scarcity of similar reports, it was not possible to establish a true overlap syndrome or casual association. When the biliary enzyme levels are elevated in patients with vasculitis, physicians should thus be mindful of the possible coexistence of these diseases.

Key words: primary biliary cirrhosis, microscopic polyangiitis, vasculitis, anti-neutrophil cytoplasmic antibodies

Introduction

Primary biliary cirrhosis (PBC) is a hepatic disease with an autoimmune pathogenesis. It is frequently associated with other rheumatic disorders such as Sjögren’s syndrome (SS), systemic sclerosis (SSc), and rheumatoid arthritis (RA). However, primary vasculitis and PBC are rarely observed concurrently. To the best of our knowledge, only six cases of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) overlapping with PBC have previously been reported (1-6).

In this report, we describe a patient with microscopic polyangiitis (MPA) involving the peripheral nerves and kidneys in whom PBC was confirmed via a biopsy, in addition to a literature review of PBC cases complicated by AAV.

We retrospectively reviewed the medical records of 54 patients who were admitted to our department for the treatment of AAV with immunosuppressive therapy between January 2006 and March 2014.

We conducted a literature review to identify cases of AAV associated with PBC. We searched the Medline database using the terms “microscopic polyangiitis,” “Wegener’s granulomatosis,” “Churg-Strauss syndrome,” “vasculitis,” or “ANCA” combined with “primary biliary cirrhosis” between 1980 and 2013. We screened the references to identify additional reports. The search was limited to cases well described in the English language literature.

We evaluated demographic data, such as age, sex, disease duration (PBC and AAV), clinical features, laboratory findings, pathological findings, and PBC and AAV management. The Ethics Committee of our institute approved this study.

Case Report

A 76-year-old man was admitted to our hospital’s Department of Gastroenterology and Hepatology in September 2005 due to symptoms of fever, decreased appetite, and abnormal laboratory findings such as elevated hepatobiliary enzymes [alkaline phosphatase (ALP), 1,469 IU/L and gamma-glutamyl transpeptidase, 184 IU/L]. He had noticed lower limb numbness in 2002, and this symptom had recently worsened. Because the inflammatory marker C-reactive protein (CRP, 7.97 mg/dL) and the erythrocyte sedimentation rate (ESR, 53 mm/hour) were elevated despite normal findings in imaging studies, such as abdominal-
pelvic computed tomography (CT), biliary infection was suspected and antibiotics were administered. However, his symptoms did not improve with this treatment, and blood cultures were negative for the presence of pathogens. Chest CT revealed a nodular shadow in the right upper lung lobe, and tissue obtained via needle biopsy under CT guidance was pathologically positive for *Mycobacterium kansasii*. The patient was thus administered antibiotics including isoniazid (INH) (300 mg/day), rifampicin (RFP) (450 mg/day), and ethambutol (EB) (750 mg/day). In addition, the patient’s myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCAs) were strongly positive (90 U/mL). Conversely, the patient’s anti-SS-A antibody and anti-SS-B antibody findings were negative. Given the abnormal urinary findings of proteinuria and microscopic hematuria, suggesting nephritis and the presence of peripheral neuropathy, we diagnosed the patient with MPA. Unfortunately, there were no findings suggestive of vasculitis in the lung tissue obtained via needle biopsy under CT guidance. Regarding the patient’s renal function, he exhibited slight renal dysfunction, with blood urea nitrogen and creatinine levels of 13.3 and 1.24 mg/dL, respectively. He was negative for hepatitis B and C infection as determined by serological testing. We began high-dose steroid therapy [prednisolone (PSL), 80 mg/day] in November of the same year. However, his inflammatory marker levels did not normalize, and thus, we started oral immunosuppressive therapy with cyclophosphamide (CPA) at an initial dose of 50 mg/day which we increased to 75 mg/day. His numbness thereafter improved, and we gradually reduced the corticosteroid dose before he was discharged. These treatments also caused a gradual decrease in the patient’s biliary enzyme levels, and his ALP level normalized to 330 IU/L at 2 months after the initiation of treatment for AAV. After 6 months, we modified his treatment from CPA to azathioprine (AZP) (100 mg/day) and reduced the PSL dose to 9 mg/day in October 2007. Follow-up chest CT performed approximately 1 year later revealed that the nodular shadow in the right upper lung lobe caused by *M. kansasii* was almost completely eliminated without any signs of aggravation after the initiation of antitubercular drug therapy. We discontinued the antibacterial drug therapy. However, the patient’s inflammatory markers continued to be weakly positive (CRP, <1.0 mg/dL) despite negativity for MPO-ANCAs. In addition, because microscopic hematuria persisted, we did not reduce the steroid dose and continued the administration of PSL (9 mg/day) and AZP (100 mg/day) for 71 months from October 2007 to August 2013. The patient’s CRP and ALP levels increased to 2.98 mg/dL and 878 U/L, respectively. In addition, abnormal casts, such as blood cell casts, appeared in the urine beginning in July 2013 (the patient was 84 years old at this time). Whole-body contrast CT and fluorodeoxyglucose-positron emission tomography performed to exclude infectious disease revealed no obvious abnormalities. We suspected exacerbation of AAV as the source of the elevated inflammatory marker levels, and we increased the patient’s PSL dose to 30 mg/day and switched from AZP to oral CPA (50 mg/day) to induce remission in September and October of the same year, respectively. However, his serum ALP and CRP levels continued to be elevated, and a liver biopsy revealed plasma cell infiltration in the portal area (Fig. 1). Moreover, based on the positive M2 anti-mitochondrial antibodies (AMAs), we diagnosed the patient with PBC associated with MPA. His serum ALP levels normalized to 226 U/L in response to ursodeoxycholic acid (UDCA) (900 mg/day) and bezafibrate (400 mg/day), although his CRP levels remained elevated at 6.75 mg/dL in November. Thereafter, we tapered the corticosteroid dose gradually. In February 2014, his PSL dose was reduced to 10 mg/day with CPA (50 mg/day), and his urinalysis was normal. The patient’s CRP levels decreased to 1.27 mg/dL. In addition, the patient’s clinical symptoms did not deteriorate. The Birmingham Vasculitis Activity Score also improved from 12 points at the time of the steroid dose increase to 0. The clinical course of the patient is summarized in Fig. 2.

**Literature review and assessment of our cases**

Our Medline search identified 6 adult patients with PBC and AAV reported between 1980 and 2013. Including our patient, we evaluated 7 patients in total. The patient ages at diagnosis were similar: 55.9±15.9 years (range: 38-83 years) for PBC and 56.1±14.3 years (range: 39-76 years) for vasculitis. Regarding the relative timing of the diagnoses of PBC and vasculitis, 2 patients were diagnosed with PBC before vasculitis, 2 were diagnosed with vasculitis before PBC, and 3 appeared to have both diseases simultaneously. Of the 7 patients studied, our patient was the only male.

In patients whose type of vasculitis was not specified in the cited articles, the types were deduced from the context of the articles and indicated as “s/o (suspected of)” as shown in Table 1. The types of AAV included MPA in 5 pa-

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**Figure 1.** Liver biopsy (Hematoxylin and Eosin staining, ×100 magnification). The portal area displayed marked plasma cell infiltration and swelling, findings consistent with PBC. Although degeneration of the bile duct epithelium was present, there were no findings to suggest either arterial branch vasculitis or granuloma.
patients, Chung-Strauss syndrome (CSS) in 1 patient, and Wegener’s granulomatosis (WG) in 1 patient. In all patients, excluding ours, vasculitis was confirmed by biopsy. All patients with MPA were positive for MPO-ANCAs or perinuclear ANCAs (P-ANCAs). Regarding inflammatory responses, all patients had positive findings for both the ESR and CRP levels. The patients’ clinical symptoms varied (Table 1).

Regarding PBC, all 6 patients with available ALP measurements exhibited an increase in their ALP levels. Immunoglobulin M (IgM) levels were also elevated in all 3 patients with available IgM measurements. All 7 patients displayed positivity for AMAs. Regarding symptoms, the majority of these patients were asymptomatic, the exceptions being 2 patients with jaundice. The liver biopsy results were consistent with findings of PBC in all 7 patients undergoing biopsy. Of 5 patients with available pathological findings, 4 had PBC stage I or II (i.e., early-stage disease) (Table 2).
Discussion

Matsumoto et al. examined liver tissue specimens obtained from 160 patients with various connective tissue diseases, reporting that PBC was observed in 9 patients (5.6%) and that AMAs were also detected in 7 patients (4.4%) (7). However, few of these patients had vasculitis. According to a cross-sectional study conducted in 5,000 patients with PBC, concurrent connective tissue diseases mainly consisted of SS (13.5%), RA (7.3%), and SSc (2.0%), although the detection rate of AMAs was high in patients with SSc and low in those with RA or SS (8). However, we cannot discount the possibility of patient differences in autoantibody reactivity to some mitochondrial proteins in those with PBC complicated by connective tissue diseases, including vasculitis, and those with PBC alone. Studies with larger sample sizes are needed to resolve this issue.

The International Chapel Hill Consensus Conference (CHCC2012) convened to improve the CHCC1994 nomenclature, change names and definitions as appropriate, and add important categories of vasculitis that were not included in CHCC1994 (9). As a result, while the terms of MPA remained unchanged, WG and CSS were changed to granulomatosis with polyangiitis (GPA) and eosinophilic GPA, respectively. Interestingly, p-ANCAs are present in 28% of patients with PBC, and their presence correlates with disease severity (10). Their pathogenic role is a matter of debate (1).

It remains uncertain whether the coexistence of development of PBC and MPA in the same patient is causal or casual. Komatsu et al. reported Goodpasture syndrome in a patient who experienced PBC for several years (11). They stated that PBC is likely not complicated by pulmonary-renal syndrome because its onset does not appear to be close to the onset of PBC. However, they also described that the immunological disturbance that activated AMAs may influence the subsequent development of pulmonary-renal syndrome, as those diseases are caused by an automechanism.

Min et al. reported a patient with PBC and systemic mononuclear inflammatory vasculopathy associated with SS who complained of cognitive dysfunction, including decreased memory, due to multiple ischemic events in the brain. Additionally, the patient developed mild weakness and numbness in both lower legs and hands due to sensory dominant vasculitic neuropathy (12). SS is the most common autoimmune disorder associated with PBC (13). Anti-Ro antibody has also been suggested to play a role in mediating the vascular damage in central nervous system disease in SS (14). The authors stated that systemic mononuclear inflammatory vasculopathy associated with SS may be an additional extrahepatic manifestation of PBC. However, among the patients in this study, and those identified in the literature review, only the patient reported by Min et al. had concurrent SS. This suggests that the causes of the vasculitis symptoms associated with PBC are likely to represent conditions other than SS. Our patient was also negative for both anti-SS-A antibody and anti-SS-B antibody, and the presence of concomitant Sjögren’s syndrome was ruled out based on his clinical symptoms. Therefore, it appears that the lower limb numbness was a symptom of mononeuritis multiplex due to MPA rather than SS.

In previous cases of PBC complicated by vasculitis, other forms of vasculitis, in addition to AAV, were also reported, including large vessel vasculititis [Takayasu’s arteritis (15-17) and giant cell arteritis (18)] and immunoglobulin A-associated vasculitis (19). Therefore, this phenomenon is not unique to AAV. In contrast, to the best of our knowledge, only 2 previous cases of concurrent MPA and PBC exist (Table 1); therefore, we believe that the present case is highly valuable. Following our patient’s initial treatment with immunosuppressive drugs, improvement of MPA was accompanied by a re-elevation of the patient’s serum ALP levels (Fig. 2), which thus suggested a possible relationship between MPA and PBC in this patient.

### Table 2. List of Patients with a Combination of PBC and AAV (PBC Details).

<table>
<thead>
<tr>
<th>No</th>
<th>Ref</th>
<th>Age</th>
<th>Symptom</th>
<th>ALP (IU/L)</th>
<th>IgM (mg/dL)</th>
<th>AMA (IF)</th>
<th>Liber biopsy</th>
<th>Treatment for PBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>83</td>
<td>Asymptomatic</td>
<td>878</td>
<td>ND</td>
<td>Positive</td>
<td>Stage I-II</td>
<td>UDCA and Bezafibrate 400mg/d</td>
</tr>
<tr>
<td>3</td>
<td>[2]</td>
<td>61</td>
<td>Probably asymptomatic</td>
<td>966</td>
<td>n.d.</td>
<td>1:5,120</td>
<td>Performed biopsy (Unkwon stage)</td>
<td>UDCA</td>
</tr>
<tr>
<td>4</td>
<td>[3]</td>
<td>66</td>
<td>Probably asymptomatic</td>
<td>1,540(50-250)</td>
<td>n.d.</td>
<td>1:640</td>
<td>CNSDC</td>
<td>UDCA600mg/d</td>
</tr>
<tr>
<td>5</td>
<td>[4]</td>
<td>38</td>
<td>Jaundice</td>
<td>471(35-110)</td>
<td>481(50-250)</td>
<td>1:200</td>
<td>Stage IV</td>
<td>UDCA12mg/kg/d</td>
</tr>
<tr>
<td>6</td>
<td>[5]</td>
<td>49</td>
<td>Jaundice</td>
<td>1,486(87-250)</td>
<td>660 (20-140)</td>
<td>1:80</td>
<td>early cirrhosis</td>
<td>UDCA600mg/d</td>
</tr>
<tr>
<td>7</td>
<td>[6]</td>
<td>39</td>
<td>Asymptomatic</td>
<td>500(30-105)</td>
<td>500(50-300)</td>
<td>strongly positive</td>
<td>Stage I</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

*1. The ages presented in this table are those of each patient at the onset of PBC.
+ Figures in parentheses are normal values.

However, considering that his biliary enzyme levels no longer improved by immunosuppressive therapy alone, during which time MPA recurred, the disease activity of MPA and PBC could not be said to correlated with one another. PBC development may in fact have been incidental. In the first previously reported case, MPA exhibited a tendency to improve in response to immunosuppressive treatment; however, the patient’s biliary enzyme levels continued to rise, and no correlation between the disease activity of MPA and PBC was observed (1). Conversely, in the second case, MPA and PBC manifested simultaneously both at the time of onset and at that of recurrence (2). The findings of these two cases are therefore conflicting, and whether or not a causal relationship exists between PBC and AAV remains uncertain. However, the various reports of concurrent AAV and PBC (1-6) suggest that PBC may worsen in terms of underlying vasculitis.

In general, corticosteroid therapy is not administered for PBC because of potential adverse reactions, such as osteoporosis, which can develop or worsen if already present (20). When underlying connective tissue disease requiring corticosteroid therapy is present, as observed in our patient, caution is required. The proper use of corticosteroids in the treatment of PBC associated with autoimmune disorders has not yet been established (21). According to the systematic review (16) concerning corticosteroid therapy for PBC performed by Prince et al., only 2 trials of inadequate power, namely Newscale 1989 (22) and Frankfurt 1999 (23-25), were identified. According to their review, serum hepatitis markers and the condition of the liver tissue were found to improve upon corticosteroid treatment, although no significant improvement in the mortality rate of these patients was observed. Moreover, the data regarding bilirubin and albumin levels related to the prognosis were insufficient. On the contrary, the number of patients with PBC experiencing side effects, as well as the extent of decreased bone mineral levels, was observed to increase by steroid therapy. However, the use of corticosteroid treatment for PBC remains controversial, and no firm conclusions regarding its utility can be drawn at present. Long-term observation of patients with PBC complicated by connective tissue disorders for which long-term corticosteroid therapy is essential, as in the present patient, may be important to resolve this issue. The elevated serum ALP level at the onset of MPA in our patient also markedly improved by immunosuppressive drug therapy, thus suggesting that steroids are effective against PBC. However, a lumber vertebral compression fracture occurred later as an adverse effect of steroid therapy. Nonetheless, in PBC patients, there appears to be no need to use steroids if UDCA and bezafibrate, which are associated with fewer adverse effects, prove to be effective.

Using the current classification criteria for vasculitis, further studies are necessary to clarify whether the association between PBC and vasculitis suggests a causal relationship or casual complication. Further studies should be conducted to investigate the mechanisms underlying the relationship of PBC with other autoimmune diseases.

An association between PBC and AAV has rarely been described, and there is currently no clear explanation for the simultaneous occurrence of both conditions. Because of the scarcity of similar reports, it was not possible to define a true overlap syndrome or a casual association. However, although the combination of PBC and AAV, including MPA, is extremely rare, it is nevertheless considered to be possible. When elevated biliary enzyme levels are found in patients with AAV, physicians should therefore be mindful of the possible coexistence of these diseases.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

This study was supported by Grants-in-Aid for Research on Intractable Diseases from the Japanese Ministry of Health, Labour and Welfare.

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