A Patient with *E. coli*-induced Pyelonephritis and Sepsis Who Transiently Exhibited Symptoms Associated with Primary Biliary Cirrhosis

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Abstract

A 28-year-old woman had chief complaints of headache and a 40°C fever. At this time, findings indicative of inflammation including elevated CRP and increased WBC were observed, and *E. coli* was detected on blood and urine culture. As a result, the patient was diagnosed with pyelonephritis and sepsis. Furthermore, markedly increased hepatobiliary enzymes and elevated anti-mitochondrial antibody were confirmed. The administration of antimicrobial agents resulted in improvement of the pyelonephritis and sepsis and normalization of hepatobiliary enzymes and anti-mitochondrial antibody levels. It has been documented that the incidence of urinary tract infection is high among patients with primary biliary cirrhosis (PBC). The findings obtained from the present patient are of considerable interest in elucidating the mechanism of onset in PBC.

Key words: *E. coli*, pyelonephritis, sepsis, primary biliary cirrhosis

Introduction

Primary biliary cirrhosis (PBC), the histopathology of which is characterized by chronic non-suppurative destructive cholangitis, often affects middle-aged women (1). Concerning the hematological findings, levels of hepatobiliary enzymes such as γ-GTP and ALP, are usually elevated in the absence of raised transaminases. At this point in time, the exact cause of PBC is not known. PBC is considered an autoimmune disease, which is closely correlated to the presence of anti-mitochondrial antibody (2).

It has been reported that the incidence of urinary tract infection, especially *E. coli*-induced recurrent urinary tract infection, is high among PBC patients, and that patients with recurrent urinary tract infection are more likely to produce anti-mitochondrial antibody M2 (3–6). In this report we present the patient who was diagnosed with *E. coli*-induced pyelonephritis and sepsis, and who exhibited findings indicative of PBC, including markedly increased hepatobiliary enzymes and elevated anti-mitochondrial antibody. As the pyelonephritis improved, levels of hepatobiliary enzymes and anti-mitochondrial antibody normalized. The findings obtained from the present patient are of considerable interest in elucidating the mechanism of onset in PBC.

Case Report

A 28-year-old woman started to develop headaches on June 10, 2001, and on around June 15, started to experience fevers sometimes reaching a temperature of 40°C and accompanied by rigors. When the patient consulted the emergency department, physical examination was unremarkable other than tenderness of the right costovertebral angle. Routine laboratory analyses showed increased CRP and WBC accompanied by shift-to-left on differential counts (WBC: 15,700/mm³, and CRP: 19.2 mg/dl) and elevated hepatobiliary enzymes (γ-GTP: 220 IU/l, ALP: 642 IU/l) (Fig. 1). However, abdominal ultrasound was negative for cholecystitis and cholangiectasis. On June 25, the patient was admitted to our department for further investigations. The patient was apyrexial at the time of admission, but developed a fever of over 38°C the following morning...
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Figure 1. Clinical course of the patient. Cultures of blood and urine revealed E. coli. Antimicrobial therapy was initiated on June 27, resulting in the fever rapidly subsiding and the inflammation resolving. The levels of ALP decreased over time and had normalized by day 35 of the illness. WBC: white blood cell count, ALP: alkaline phosphatase, AMA: anti-mitochondrial antibody, AMK: Amikacin, CTRX: Ceftriaxone, CEZ: Cefazolin, CCL: Cefaclor.

However, no other vital signs were abnormal. Apart from the persisting tenderness of the right costovertebral angle, no other notable findings were detected on physical examination. On clinical laboratory tests on admission, findings indicative of inflammation were confirmed: WBC: 8,800/mm³ (My 3%, St 4%, and Seg 64%), CRP 4.4 mg/dl, erythrocyte sedimentation rate 100 mm/h, and urinary WBC 21–50/high power field. Moreover, although the levels of γ-GTP and ALP were elevated at 371 and 1,308 IU/ml, respectively, no marked increases in transaminases or bilirubin were apparent (GOT: 31 IU/ml, GPT: 47 IU/ml, total bilirubin: 0.4 mg/dl). Furthermore, while the level of anti-mitochondrial antibody was elevated (titer: 40), the level of the M2 subtype of anti-mitochondrial antibody was not (titer: <5.0). Anti-nuclear antibody and anti-thyroglobulin antibody were negative. Cultures of blood and urine revealed E. coli. No abnormality was seen on the thoracoabdominal X-ray examination. Abdominal ultrasound showed mild enlargement of the left kidney, but no sign indicative of hydronephrosis was seen. Additionally, while mild splenomegaly (58x44 mm) was observed, signs indicative of hepatic, biliary or pancreatic abnormality, such as cholangiectomy, were absent.

Because E. coli was detected on blood and urine cultures, the patient was diagnosed with pyelonephritis and sepsis. Antimicrobial therapy was initiated on June 27, resulting in the fever rapidly subsiding and the inflammation resolving. Regarding hepatobiliary enzymes, while the levels of γ-GTP and ALP remained elevated. Since repeat abdominal ultrasound revealed no obstruction and the level of anti-mitochondrial antibody was mildly elevated, primary biliary cirrhosis (PBC) was strongly suspected. However, levels of anti-mitochondrial antibody M2, which are a more specific indicator of PBC, were not elevated. The patient was discharged once the inflammation had ameliorated, and antimicrobial agents were administered on an outpatient basis. Levels of γ-GTP and ALP decreased over time and had normalized by day 35 of the illness. In January 2002, about six months after the onset, levels of the hepatobiliary enzymes remained normal, and the level of anti-mitochondrial antibody was confirmed to be normal (<20).

Discussion

The present patient was diagnosed with E. coli-induced pyelonephritis and sepsis, and exhibited findings indicative of PBC, including markedly increased hepatobiliary enzymes and elevated anti-mitochondrial antibody. As the pyelonephritis improved, levels of hepatobiliary enzymes and anti-mitochondrial antibody normalized.

It is well-known that sepsis often accompanies liver dysfunction, and the elevation of hepatobiliary enzymes, including γ-GTP and ALP, can be observed. However, it is reported in the reviews on the association between bacteremia and liver dysfunction that the elevated ALP levels induced by sepsis remain below 450 IU/ml, if there are no other factors that worsen abnormalities of liver enzymes such as multiple organ failure (7, 8). Since the ALP level was above 1,000 IU/ml in the present patient, we can speculate that there were some factors other than sepsis causing the elevation of ALP. In addition, we also examined the levels of hepatobiliary enzymes in 68 patients with sepsis who were admitted to our hospital (Fig. 2). The levels of mean ALP and γ-GTP in patients with sepsis were 347 IU/ml and 148 IU/ml, respectively, and the levels of ALP and γ-GTP in the present patient were considered to be extremely high. Taken together, we speculate that the elevation of hepatobiliary enzymes is probably due to PBC-like symptoms rather than cholestasis in sepsis, although the possibility that the elevation of ALP and γ-GTP in this patient is due to cholestasis in sepsis cannot be excluded completely.

PBC often affects middle-aged women, and is characterized by general malaise, pruritus, jaundice, and hepatomegaly. The condition generally advances to liver cirrhosis over time, ranging from several years to decades. Concerning hematological findings, levels of hepatobiliary enzymes such as γ-GTP and ALP, are usually elevated in the absence of raised transaminases. As PBC advances, the level of bilirubin also increases. Furthermore, the histopathology of PBC is characterized by chronic non-suppurative destructive cholangitis (1).

At this point in time, the exact cause of PBC is not known. There are some reports that infectious agents themselves are related to the pathogenesis of PBC and their DNAs are detected by PCR in the liver of some patients, but...
Furthermore, increased anti-mitochondrial antibody ducts, the patient's symptoms appeared to be associated with 
firmly. Also, since an abdominal ultrasound failed to dem-
strate any abnormality, including dilatation of biliary 
ducts, the patient's symptoms appeared to be associated with PBC. Furthermore, increased anti-mitochondrial antibody strongly supported this also. Consideration of these factors suggested that symptoms were associated with PBC. However, the patient tested negative to anti-M2 antibody. This could represent a false-negative result, due to the low 
sensitivity, as discussed previously. Further studies such as immunoblotting for the possible antigens for M2 might be required to exclude the possibility that anti-M2 antibody is negative for this patient, and histological examination is also important to diagnose the present patient with PBC.

Furthermore, in the present patient, the levels of hepatobiliary enzymes increased during episodes of pyelonephritis, then normalized as the pyelonephritis was alleviated, suggesting that the renal inflammation was involved in the onset of the PBC-like symptoms in the present patient. Interestingly, a study found that the incidence of urinary tract infection among patients with PBC, with other chronic hepatopathies, and with rheumatoid arthritis (RA) was 19%, 7% and 8%, respectively (3). Moreover, in another study, the incidence of urinary tract infection in healthy women, age-matched with PBC patients, was 5% (4). These findings suggest that the incidence of urinary tract infection among PBC patients is high. In addition, E. coli accounts for about 70% of urinary tract infections accompanying PBC (3). One study found that urinary tract infection was recurrent in about 60% of PBC patients, and that recurrence was due to the same organism, generally E. coli (5). Another study documented that about half of women, who did not have hepatopathy but were taking preventative antimicrobial therapy due to a past history of recurrent urinary tract infection, showed decreased anti-mitochondrial antibody M2 production (6). These findings suggest that the incidence of increased anti-mitochondrial antibody M2 in women with a past history of recurrent urinary tract infection is markedly higher than that in patients with other chronic hepatopathies, or in healthy individuals. The above findings imply that the incidence of urinary tract infection, especially recurrent urinary tract infection induced by E. coli, is high among PBC patients, and that patients with recurrent urinary tract infection are more likely to produce anti-mitochondrial antibody M2. In other words, a possible mechanism of onset in PBC can be suggested by these epidemiological findings; that E. coli-induced recurrent urinary tract infection induces the production of anti-mitochondrial antibody, ultimately contributing to the development of causing PBC. As it has been reported that some kinds of autoantibodies, like rheumatoid factors and antinuclear antibodies, can be detected frequently in the serum of patients with infectious diseases including urinary tract infections (14), the relationship between infections and autoantibodies should be interpreted very cautiously. However, taking those epidemiological findings into account, the mechanism by which E. coli-induced recurrent urinary tract infection causes the production of anti-mitochondrial antibody, ultimately contributing to the development of causing PBC, cannot be excluded.

Another factor related to the involvement of E. coli in the onset of PBC is the molecular homology between E. coli and humans. Molecular homology is believed to play an important role in the activation of autoreactive T cells (15, 16), and this activation could actually be the cause of several autoimmune diseases (17, 18). It has been reported that, in

![Figure 2. Serum ALP and γ-GTP levels in 68 patients with sepsis who were admitted to the University of Tokyo Hospital in April and May 2003. Serum samples were collected when examination of blood cultures were performed. +: patient's data, X: mean. Bars denote 99% confidence interval.](image-url)
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PBC patients, the antigens that trigger production of antimitochondrial antibody are two mitochondrial proteins (70 and 45 kDa proteins) (19). The 70 kDa protein is believed to be the pyruvate dehydrogenase complex (PDC), which is one of the constituents of the 2-oxo acid dehydrogenase complex (E2) (20). Several studies have reported the expression of the pyruvate dehydrogenase complex in the E2 component (PDC-E2) or molecules that cross-react with PDC-E2 to be elevated in the biliary epithelial cells of PBC patients (21, 22). Furthermore, the level of T cells reactive to PDC-E2 in the peripheral blood of PBC patients has been reported to be higher than that of healthy individuals (23), and T cells reactive to the 163–176 peptides of human PDC-E2 have been found in the liver and porta hepatis lymph nodes of PBC patients (24). These findings suggest that PDC-E2, particularly the 163–176 peptide region, is an important antigen for the onset of PBC. Furthermore, peptides originating from E. coli PDC-E2 activated T cells are reactive to human PDC-E2 163–176 peptides (25), and as a result, the molecular homology between E. coli and human PDC-E2 has been hypothesized (24). According to this theory, cross-reactivity between these two complexes could lead to the onset of PBC (24). These findings suggest that antibodies produced by recurrent E. coli infection, which should only react with E. coli PDC-E2, cross-react with human PDC-E2. In other words, these antibodies have been called “anti-mitochondrial antibodies” associated with PBC, and ultimately cause PBC.

However, it has been reported that the production of antimitochondrial antibody alone is not sufficient to induce PBC. In other words, even when the production of anti-mitochondrial antibody is induced by the (repeated) administration of a recombinant E2 component, chronic non-suppurative destructive cholangitis, which is thought to be typical of PBC, is not induced in a sustained manner (26). On the other hand, chronic non-suppurative destructive cholangitis has been reported to be induced by the following stimuli: inoculation of a PDC-E2/BCKD-E2 hybrid molecule; administration of lipopolysaccharide and adjuvant to mice that had undergone a thyroidectomy soon after birth; or immunization with PDC or PDC-E2/E3 BP (27, 28). As a result, continuous non-suppurative destructive cholangitis can be induced only when production of anti-mitochondrial antibody is combined with some type of immunological dysregulation. Moreover, several studies have reported that the incidence of PBC among those with a family history of PBC is several hundred times higher when compared to the general public (29, 30), thus suggesting the involvement of genetic factors in the onset of PBC. It is highly possible that susceptibility to immunological dysregulation could be genetically determined.

Regarding the mechanism of onset of the transient PBC-like symptoms during an episode of E. coli-induced pyelonephritis in the present patient, we can advance the hypothesis below. Infection with E. coli induced the production of antibodies against E. coli PDC and other bacterial components, and anti-mitochondrial antibody reactive to PDC in biliary epithelial cells was produced due to cross-reactivity. This lead to the onset of clinical symptoms associated with cholangitis and increased the levels of hepatobiliary enzymes. However, as the patient did not have the immunological dysregulation, anti-mitochondrial antibody was not continuously produced, and cholangitis improved and levels of the hepatobiliary enzymes normalized in parallel with resolution of the bacterial infection.

At present, numerous studies are being conducted to ascertain the mechanism of onset of autoimmune diseases, but many points remain unknown. The results obtained from the present case are of considerable interest in ascertaining the mechanism of onset of PBC, which is considered an autoimmune disease. A further point of note is that, as levels of hepatobiliary enzymes are not usually measured in patients with urinary tract infection, these enzymes may be latently high in many other patients with urinary tract infection. Patients with clinical features similar to those seen in the case presented should form the subjects of future investigations in order to elucidate the mechanism of onset of PBC and to develop effective therapy for this disease.

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References


