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Type: Case Report

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Key words: hemocholecyst, hemodialysis, microscopic polyangiitis

Abstract

Microscopic polyangiitis (MPA) is a systemic vasculitis associated with antineutrophil cytoplasmic antibodies, and it involves multiple organs, including the kidneys and lungs. We report on the case of a 72-year-old woman with MPA who developed hemocholecyst in addition to alveolar hemorrhage and rapid progressive glomerulonephritis. Although her renal function was not salvaged, the alveolar hemorrhage and hemocholecyst were conservatively treated. Clinicians should consider the possibility of hemocholecyst in patients with MPA complaining of abdominal pain.

Introduction

Microscopic polyangiitis (MPA) is a systemic vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA). Although the commonly affected organs include the kidneys and lungs, the involvement of the gallbladder (i.e., cholecystitis) rarely occurs in patients with MPA [1–3]. However, to our knowledge, this is the first case report of patients with MPA who developed hemocholecyst.

We report on the case of a 72-year-old woman with MPA who developed hemocholecyst in addition to alveolar hemorrhage and rapid progressive glomerulonephritis (RPGN). Her renal function was not salvaged, so she had to continue hemodialysis; however, the alveolar hemorrhage and hemocholecyst were conservatively and successfully treated. We present the patient's clinical course and consider the relationship between the hemocholecyst and MPA.

Case Report

The patient was a 72-year-old-woman without any significant past medical history. She had not mentioned abnormal urinalysis or renal dysfunction before. She experienced hemosputum in addition to general fatigue and anorexia. A month later, in addition to these symptoms, she presented with severe anemia and renal dysfunction; thus, she was referred to our hospital.

On admission, the patient's blood pressure was 162/78 mmHg, pulse was 80 beats/min, and percutaneous oxygen saturation level was 96% on 3 L/min of oxygen administered via nasal cannula. The physical examination revealed fine crackles on chest auscultation and edema of the lower limbs. There were neither skin rashes nor signs of arthritis. The laboratory data were as follows: white blood cell count, 7,540 μL with 92.9% neutrophils, 3.8% lymphocytes, 2.8% monocytes, 0.1% eosinophils and 0.4% basophils; hemoglobin, 5.2 g/dL; platelet, 24.7×10^4 μL; lactate dehydrogenase, 321 IU/L; blood urea nitrogen, 113.0 mg/dL; creatinine, 12.9 mg/dL; potassium, 6.6 mEq/L; C-reactive protein, 7.85 mg/dL; and myeloperoxidase (MPO)-ANCA, 16.8 U/mL. The proteinase 3-ANCA and anti-glomerular basement membrane antibodies were negative. Additionally, the surfactant protein D and KL-6 levels were within the normal range. The urinalysis revealed hematuria and proteinuria with epithelial casts. The electrocardiography was normal. The renal ultrasonography demonstrated no significant atrophy. A chest radiograph and computed tomography (CT) revealed diffuse ground-glass

opacity in both lower lung fields. According to both these imaging findings and the hemosputum, alveolar hemorrhage was strongly suspected. Although bronchoalveolar lavage was essential to diagnose, the patient's condition was so unstable that she did not undergo the examination. Thus, we clinically diagnosed the alveolar hemorrhage without bronchoalveolar lavage. Based on these findings such as the alveolar hemorrhage, RPGN, and positive MPO-ANCA, we made a diagnosis of MPA.

Figure 1 presents the patient's clinical course. The patient received methylprednisolone intravenously (1 g/day) for three days followed by prednisolone (PSL) (60 mg/day) with simultaneous blood transfusion. Additionally, the patient started to receive hemodialysis three days per week because of renal dysfunction. Unfortunately, the patient gradually developed respiratory failure due to the alveolar hemorrhage and required mechanical respiratory support with bi-level positive airway pressure on day 5. We regarded this condition as an extremely severe case of MPA and performed plasma exchange for three consecutive days from days 5–7. Fortunately, the inflammatory reaction immediately improved within the normal range, and the patient was weaned from the mechanical ventilation on day 14. Subsequently, the PSL dose was gradually tapered to 40 mg/day. However, on day 39, the patient began complaining of abdominal pain in the right upper quadrant of the epigastrium with Murphy's sign and peritoneal irritation, including rebound tenderness and muscular defense. The laboratory data revealed a rapid decline in hemoglobin and an increase in hepatobiliary enzymes (Table 1), and the other data were as follows: platelet, 8.6×10^4 μL; prothrombin time, 11.9 sec; international normalized ratio, 0.96; and activated partial thromboplastin time, 45.8 sec. An abdominal ultrasonography revealed a highly echogenic mass in the gallbladder, and a CT revealed a high-density mass in the distended gallbladder (Figure 2a). From these findings, we made a diagnosis of hemocholecyst, which was accompanied by a biliary obstruction. Since the patient's condition prevented any operative treatment, we decided to use conservative treatments, including fasting, antimicrobial therapy (cefoperazone/sulbactam, 1 g/day), and blood transfusion. The total bilirubin increased up to 6.0 mg/dL, and hemostasis spontaneously occurred, causing the patient to gradually improve with no complications, such as cholecystitis or cholangitis. Although the patient had to continue hemodialysis, she was discharged independently. Three months later, we re-evaluated the gallbladder by using CT, which demonstrated no structural abnormalities, i.e., no hematomas, tumors,

or stones (Figure 2b).

Discussion

Our patient with MPA had two severe symptoms (i.e., alveolar hemorrhage and hemocholecyst) that were conservatively treated, although her renal function was not salvaged. MPA is a systemic vasculitis associated with ANCA, which mainly affects the kidneys and lungs. Gastrointestinal involvement occurs in various vasculitides; however, gallbladder involvement such as cholecystitis rarely reported in patients with MPA [1–3]. One possible explanation why the gallbladder is damaged by vasculitides including MPA is that the gallbladder differs in the lack of muscular layer of mucosa and submucosal layer from other gastrointestinal tracts, which means inflammation of blood vessel walls could spread in the gallbladder. Another explanation is that the gallbladder is vulnerable to ischemia, because its blood flow is supplied through the cystic artery as a terminal artery [4, 5].

Hemocholecyst, which refers to bleeding confined to the gallbladder, is quite rare but is caused by various etiologies [6, 7]. The main causes of hemocholecyst include cholecystitis, tumors, and iatrogenic complications. Other rare causes include anticoagulation therapy, hemodialysis, and vasculitides [7–9]. Anticoagulation therapy can cause hemocholecyst similarly to gastrointestinal bleeding. In hemodialysis patients, bleeding is triggered by the use of anticoagulant drugs and the uremic syndrome. In vasculitides, systemic lupus erythematosus (SLE), Henoch-Schönlein purpura, and polyarteritis nodosa have been reportedly cause hemocholecyst. However, to our knowledge, this rare symptom has not yet been reported in patients with MPA. Since our patient did not receive a cholecystectomy or a pathological examination, the accurate etiology is unknown; thus, the cause of bleeding was either due to MPA, hemodialysis, or another factor. However, the CT images taken three months after the onset of the hemocholecyst demonstrated no structural abnormalities such as tumors or stones. The onset was when the anticoagulation in hemodialysis was changed from a low molecular weight heparin to an unfractionated heparin, suggesting that the cause was due to hemodialysis. There is a case report on hemocholecyst in a patient with highly active SLE, which pathologically demonstrated bleeding from the full thickness of gallbladder wall, infiltration cells to small arteries under the muscular layer and destroyed internal elastic lamella on Elastica van Gieson stain [10]. This

report showed the association between disease activity and vasculitis associated hemocholecyst. Although various factors including MPA and hemodialysis were complicated in the present case, MPA in itself might be less likely to be related to hemocholecyst because corticosteroid therapy and plasma exchange significantly reduced the body's inflammatory response.

In principle, open cholecystectomy or laparoscopic cholecystectomy is selected as a first line treatment for hemocholecyst. Other options include transarterial embolization (TAE), percutaneous transhepatic gallbladder drainage (PTBD), or endoscopic nasobiliary drainage (ENBD) [11]. In our case, the patient had respiratory failure and MPA, and she received hemodialysis and corticosteroid therapy. Therefore, we did not think that she would be able to undergo general anesthesia or an operation. Next, we considered the potency of TAE; however, this treatment can necrotize the gallbladder, and as a rule, its therapy is selected to control of bleeding and to create a bridge for cholecystectomy. PTBD was unfavorable in this patient, because she had MPA and received hemodialysis, which could easily cause bleeding. ENBD was a good option for this patient, and we were going to perform this therapy if she had not endured pain or developed an infection, which was not controlled by this conservative treatment. Fortunately, we successfully treated her without the aforementioned therapies and used other conservative treatments such as fasting and antimicrobial therapy, which are therapeutic options for patients with severe conditions such as in our case.

ANCA associated vasculitides (AAV) are one of the most critical causes leading to end stage renal disease [12, 13]. Although it was reported in some studies that patients with AAV had a significantly lower relapse rate after the initiation of chronic dialysis than that before, monitoring the activity of the other organs is necessary [14, 15]. It is generally important to carefully examine patients with AAV and to detect organ specific symptoms with scoring systems such as Birmingham Vasculitis Activity Score, Vasculitis Damage Index and 36-item Short Form [16]. However, frequent misdiagnoses, leading to wrong or late treatment and fatal prognosis, have been problems. For example, an intestinal vasculitis can lead to symptoms that mimic peritonitis in peritoneal dialysis patients, and a pulmonary hemorrhage can lead to symptoms that mimic pulmonary edema in hemodialysis patients [17]. Although ANCA measurements are controversial to predict future disease relapse, those are often performed and recommended to check during remission [16, 18]. Still, ANCA

are prone to false positives in hemodialysis patients [19]. Thus, treatment should not be escalated solely on the basis of an increase in ANCA [16].

Disease relapse are often observed in patients with AAV. In the guidelines, a minor relapse should be treated with an increase in prednisolone dosage and optimization of concurrent immunosuppression. A major relapse should be treated with rituximab or cyclophosphamide with an increase in prednisolone. The addition of intravenous methylprednisolone or plasma exchange may also be considered [16]. Although there are no guidelines especially for dialysis patients with AAV, both dialysis and AAV are strong risk factors for infection; thus potent immunosuppressive therapies should be avoided [14, 20, 21].

Despite the advance in therapy for AAV, the prognosis in dialysis patients with AAV remains controversial. Some studies showed that AAV patients with dialysis had a higher death rate compared to those without dialysis [14, 20], suggesting that the combination of AAV and ERSD is related to poor prognosis. On the other hand, Romeu et al. [21] reported there was no significant difference in cardiovascular death rate between AAV and non-AAV patients on chronic dialysis, which means AAV in itself may not be a risk factor for mortality in patients on chronic dialysis. Therefore, further studies with a larger group of patients are needed to examine the possible relationship between the mortality and AAV in patients on chronic dialysis.

Risk factors for relapse of AAV especially in dialysis patients are unclear. Walsh et al. [22] reported that patients with AAV including cardiovascular manifestations had a significantly higher relapse rate, even though those are difficult to diagnose and contribute clearly to AAV. Thus, evaluation of cardiovascular status in AAV patients on chronic dialysis could be beneficial to improve relapse prediction and prognosis of AAV.

In conclusion, clinicians should consider the possibility of hemocholecyst in patients with MPA who complain of abdominal pain. The further accumulation of cases and studies are necessary to clarify the relationship between MPA and hemocholecyst.

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Conflict of interest

None.

Tables

Table 1. Laboratory data before and after at the onset of hemocholecyst

	Before (day 34)	After (day 39)
WBC count (μL)	7,540	6620
Hemoglobin (g/dL)	12.2	8.1
Platelet (μL)	24.7×10^4	8.4×10^4
CRP (mg/dL)	7.85	0.12
PT-INR	1.11	0.96
APTT (sec)	28.1	45.8
MPO-ANCA (U/mL)	16.8	1.0
T-Bil (mg/dL)	0.8	3.0
ALP (IU/L)	152	944
AST (IU/L)	19	559
ALT (IU/L)	20	416

WBC white blood cell. *CRP* C-reactive protein. *PT-INR* prothrombin time-international normalized ratio. *APTT* activated partial thromboplastin time. *MPO-ANCA* myeloperoxidase antineutrophil cytoplasmic antibody. *T-Bil* total bilirubin. *ALP* alkaline phosphatase. *AST* asparatate aminotransferase. *ALT* alanine aminotransferase

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Figure legends

Figure 1. Clinical course. *m-PSL* methylprednisolone. *PSL* prednisolone. *HD* hemodialysis. *T-Bil* total bilirubin. *CRP* C-reactive protein. *Hb* hemoglobin

Figure 2. Computed tomography images at the onset of hemocholecyst **(a)** and three months after the onset of hemocholecyst **(b)**

Figure 1

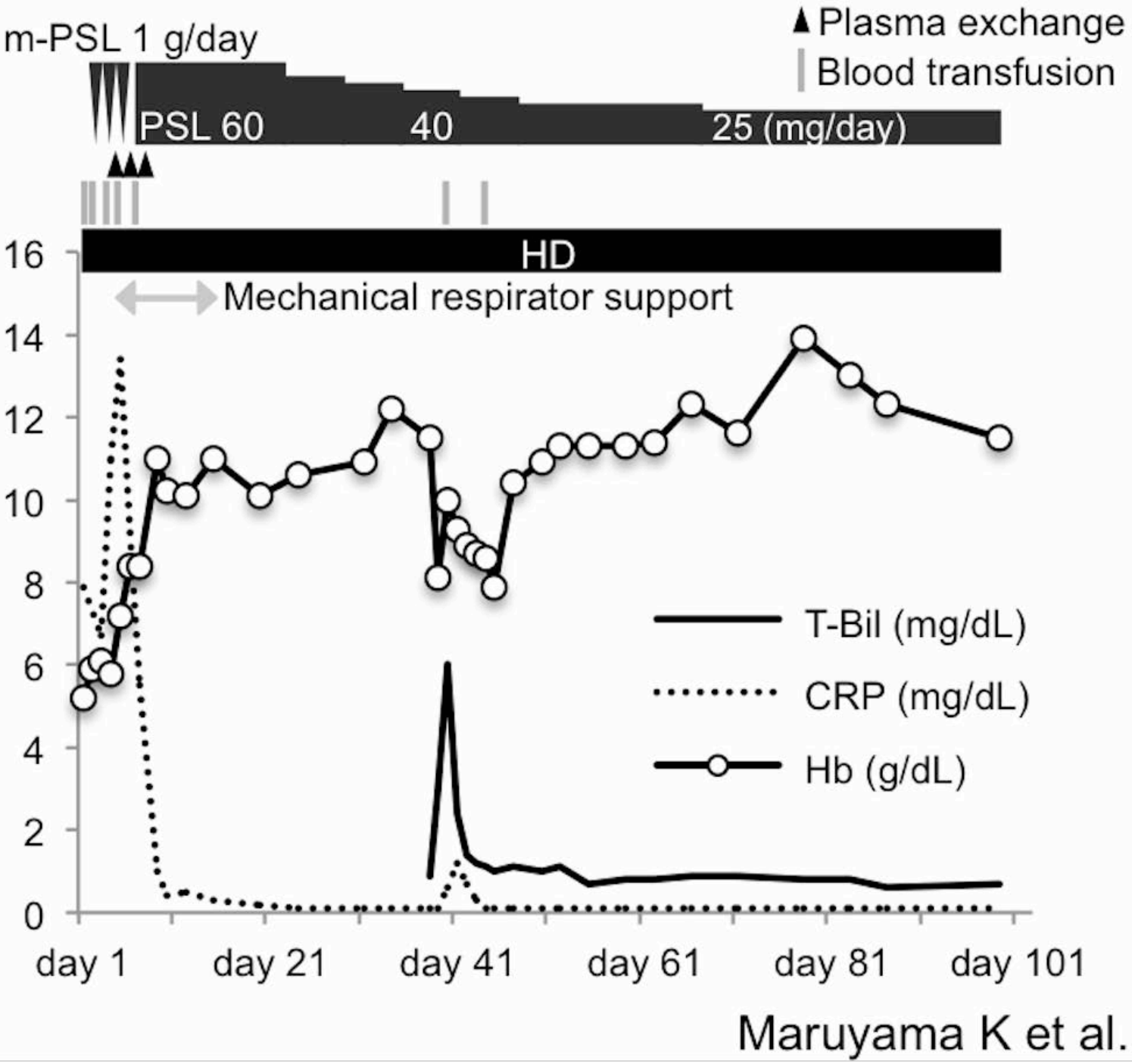

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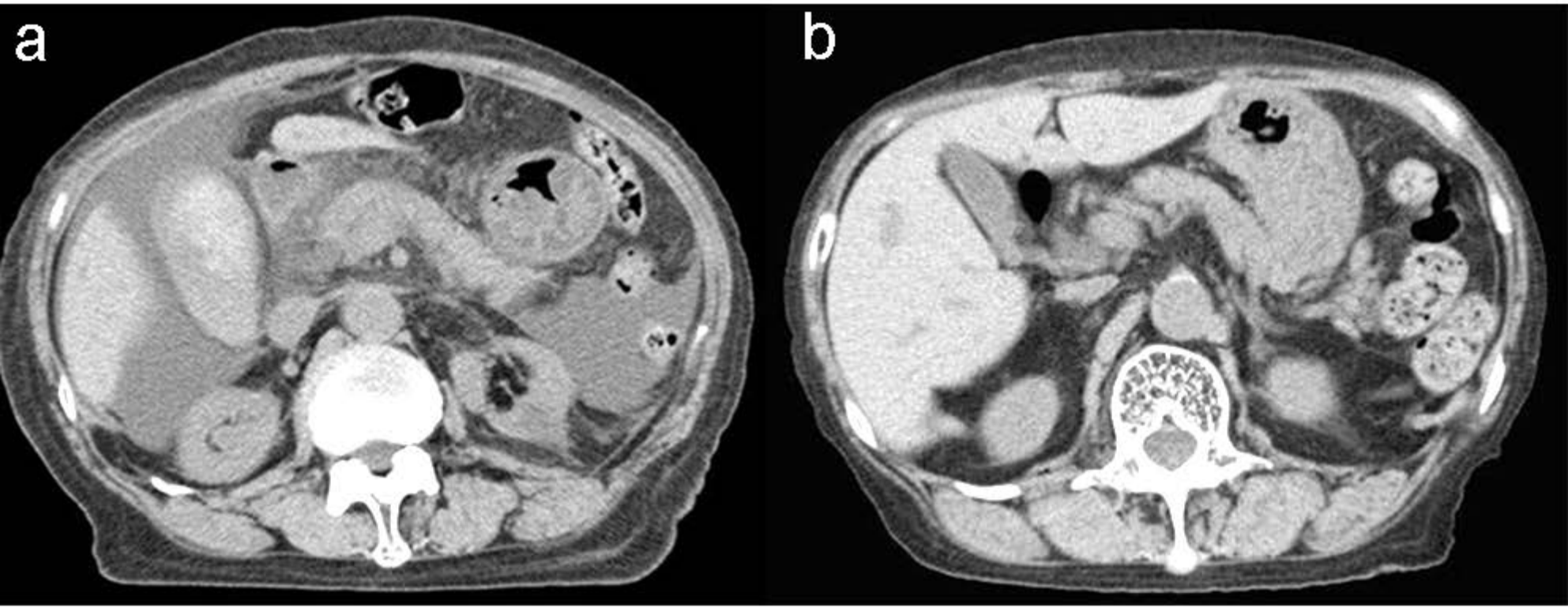
Figure 2



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