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Case Report

Nontraumatic Spontaneous Bilateral Renal Hemorrhages (Wünderlich Syndrome) with Chronic Infection of *Chlamydia Pneumonia*: A Case Report

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ABSTRACT

Introduction: Nontraumatic spontaneous renal hemorrhage is caused by tumor such as renal cell carcinoma or angiomyolipoma in most cases. Vasculitis including periarteritis nodosa or Antineutrophil Cytoplasmic Antibody (ANCA)-mediated vasculitis may also be the next underlying background. Here in, we report the first case of nontraumatic spontaneous bilateral renal hemorrhage combined with chronic infection of *Chlamydia pneumoniae*.

Case presentation: The patient serially suffered from left and right back pain within 78 days due to bilateral spontaneous renal hemorrhages. Transcatheter arterial embolization was successfully performed twice to treat serial spontaneous bilateral renal hemorrhages. The serological examination apparently revealed his chronic infection of *Chlamydia pneumoniae* and a slight elevation of anti-deoxy nucleotide antibodies. Furthermore, Computed Tomography (CT) angiogram and ^{67}galium citrate scintigram also suggested underlining severe arteriosclerosis without severe inflammation in bilateral kidneys. Chronic infection of *Chlamydia pneumoniae* and underlying autoimmune vasculitis may pull a trigger of bilateral spontaneous renal hemorrhages although the real mechanisms remain unknown.

Conclusions: In conclusion, we reported an extremely rare case of nontraumatic spontaneous bilateral renal hemorrhage of unknown etiology. Severe atherosclerosis caused by chronic infection due to *Chlamydia pneumoniae* may predispose to the vascular vulnerability of the bilateral renal arteries in close association with hypertension, oral intake of antiplatelets, and underlying autoimmune vasculitis.

Keywords: Atherosclerosis; Angiomyolipoma; Kidney neoplasm; Periarteritis nodosa; Autoimmune vasculitis

Abbreviations: RBC: Red Blood Cell; WBC: White Blood Cell; FFP: Fresh-Frozen Plasma; BUN: Blood Urea Nitrogen; TAE: Transcatheter Arterial Embolization; BPM: Beats Per Minute; PCI: Percutaneous Coronary Intervention; ANA: Antinuclear Antibody; PAN: Polyarteritis Nodosa; ANCA: Antineutrophil Cytoplasmic Antibody; Hb: Hemoglobin; Plt: Platelets; PT-INR: Prothrombin Time-International Ratio; APTT: Activated Partial Thrombin Time; AST: Aspartate Aminotransaminase; ALT: Alanine Aminotransaminase; γ-GTP: Gamma-Glucose Transpeptidase; LDH: Lactate Dehydrogenase; TP: Total Protein; Alb: Albumin; CRP: C-Reactive Protein; RF: Rheumatoid Factor; MPO-ANCA: Myeloperoxidase-Antineutrophil Cytoplasmic Antibody; PR3-ANCA: Proteinase-3-Antineutrophil Cytoplasmic Antibody; anti-ssDNA Ab: anti-single-strand Deoxy Nuclease Antibody; anti-ds DNA Ab: anti-double-strand Deoxy Nuclease Antibody. DPB: Diffuse Panbronchiolitis; COPD: Chronic Obstructive Lung Disease; Crea: Creatinine; FDP: Fibrin/Fibrinogen Degradation Products

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INTRODUCTION

Nontraumatic spontaneous renal hemorrhage is a very rare disease that can be fatal in some cases. The underlying primary diseases that cause secondary renal hemorrhage include malignant tumor, vasculitis, and infection. In this report, we presented our experience on an extremely rare case of bilateral renal hemorrhage that occurred twice consecutively in a short span of time [1-6].

CASE PRESENTATION

A 72-year-old man was transferred from a nearby hospital because of sudden onset of severe left back pain, which was caused by a large left subrenal hematoma, as shown on Computed Tomography (CT). He had a history of percutaneous coronary intervention 19 months ago for angina pectoris, for which he took combination tablets of aspirin and clopidogrel.

Laboratory Tests	Values	Laboratory Tests	Values	Laboratory Tests	Values
WBC	1.77 × 10^4/μL	AST	30 U/L	RF	<3.0 IU/mL
RBC	3.69 × 10^6/μL	ALT	26 U/L	MPO-ANCA	<1.0 U/mL
Hb	11.1 g/dL	γ-GTP	67 U/mL	PR3-ANCA	<1.0 U/mL
Plt	23.9 × 104/μL	LDH	226 U/L	ANA	× 40
FDP	4.0 mg/mL	TP	5.4 g/dL	anti-ss DNA Ab	2.3 IU/mL
D-dimer	2.1 mg/mL	Alb	3.0 g/dL	anti-ds DNA Ab	4.8 IU/mL
PT-INR	1.05	BUN	32 mg/dL	Ferritin	84.0 ng/mL
APTT	25.7 sec	Crea	2.12 mg/dL	CRP	<0.3 mg/dL

Table 1: Laboratory data at the first admission. **Note:** The underlined data are abnormal values.

He had no family history of coagulopathy or hematopoietic disorders.

On admission, the patient had a Glasgow coma scale of E4V5M6, with body temperature of 36.5°C, respiratory rate of 26 breaths per minute, blood pressure of 147/54 mmHg, and regular pulse rate at 94 beats per minute. His back pain was localized to the left flank, and the abdomen was rigid. Laboratory examination revealed a Red Blood Cell (RBC) count of 369 × 106 /l, White Blood Cell (WBC) count of 17,700 /,l and hemoglobin of 11.1 g/dl. Despite the slight renal dysfunction, based on Blood Urea Nitrogen (BUN) of 32 mg/dl and creatinine of 2.12 mg/dl (Table 1), a contrast CT scan was performed and detected active bleeding in the left renal artery inside the massive hematoma in the left kidney (Figure 1A). Because of the presence of extravasation around the left kidney, we decided to perform an angiogram with Transcatheter Arterial Embolization (TAE) immediately after the contrast CT scan.

On angiogram, there was clear massive extravasation of contrast media, which signified active bleeding from a branch of the left renal artery; TAE was performed with gelatin sponges (Figure 1B). Massive blood transfusion of a total of 10 units of both packed RBC and FFP was necessary during and after TAE because the patient went into shock. In addition, he developed acute renal failure and bacterial pneumonia after TAE. For a few days after TAE, mechanical ventilation and continuous hemodialysis filtration were utilized to support oxygenation and hemodynamics, in conjunction with intravenous antibiotics. Notably, on day 9 after the first admission, the patient suddenly developed thromboembolic occlusion of the right central retinal artery. Vasculitis was highly suspected because of the inflammatory symptoms of fever, leukocytosis, and high level of C-reactive protein, in combination with renal hemorrhage and retinal arterial thrombosis. However, the negative test of immunologic markers such as C3, C4, CH50, RF, cytoplasmic antineutrophil cytoplasmic antibody (CPO-ANCA), and myeloperoxidase antineutrophil cytoplasmic antibody (PR3-ANCA) ruled out ANCA-associated vasculitis. As other immunological markers including Antinuclear Antibody (ANA), anti-single strand, and anti-double-strand4 deoxynucleotide (ssDNA/ds DNA) antibodies were slightly elevated (Table 1), we suspected that autoimmune vasculitis could be concealed

behind the background of spontaneous bilateral renal hemorrhages. Although the recovery was slow, the patient was successfully discharged from the hospital 63 days after the first admission.

However, 15 days after discharge, the patient was readmitted to the hospital because of right back pain and hemorrhagic shock secondary to bleeding in the contralateral kidney. Repeat TAE with both metallic coils and n-butyl-2 cyanoacrylate (Histoacryl R, B Braun Aesculap, Tokyo, Japan) was successful in stopping the bleeding from the right kidney. Although we planned on obtaining renal biopsy specimens for further investigation of the vascular pathology, needle biopsy or nephrectomy was not performed as both diagnostic and therapeutic choices. On further workup, CT angiography showed no aneurysm formation or vascular occlusion. However, CT angiography also revealed many subendothelial plaque formations in the abdominal aorta, suggesting severe atherosclerosis of the aorta and its branches. Furthermore, ^{67}gallium citrate (^{67}Ga) scintigraphy revealed no abnormal accumulation, suggesting the absence of severe inflammation and malignancy in the systemic organs. The patient was finally discharged from the hospital 37 days after the second admission (115 days after the first admission).

As severe atherosclerosis was observed in the CT angiogram, we measured immunological titer of anti-*Chlamydia pneumoniae* antibodies (IgA, IgG, and IgM) during and after the second admission because *Chlamydia pneumoniae* infection is closely related to atherosclerosis. Three indexes (IgA, IgG, and IgM) of an anti-*Chlamydia pneumoniae* antibody were elevated; therefore, oral administration of Clarithromycin (CAM, 400 mg/day, twice daily) was initiated for the prevention and treatment of spontaneous renal hemorrhage and continued for 198 days. However, the titers of anti-*Chlamydia pneumoniae* antibodies were not significantly altered after a long-term CAM therapy (Figure 1C). Neither pulmonary infiltration nor ground-glass opacity of interstitial pneumonia caused by *Chlamydia pneumoniae* occurred during two admissions (data not shown).

RESULTS AND DISCUSSION

Spontaneous nontraumatic renal hemorrhage was first documented in the literature by Bonet in 1700 as a rare disease, although it was again reported as Wünderlich syndrome by a German doctor in 1856 [1-13]. Spontaneous bilateral renal hemorrhage is extremely rare because it is unlikely to occur in the absence of anticoagulant or antiplatelet intake when it occurred consecutively not simultaneously [14]. In our case, the first event of the renal hemorrhage occurred when the patient took clopidogrel (oral antiplatelet) daily, and the second event of renal hemorrhage occurred only 15 days after the first hospital discharge.

Several researchers reported the etiology of nontraumatic spontaneous renal hemorrhage. Most cases were caused by vascular proliferative tumors, such as renal cell carcinoma or angiomyolipoma (57–73%) or choriocarcinoma, followed by autoimmune vasculitis including Polyarteritis Nodosa (PAN) or segmental arterial mediolysis [1-7]. In particular, spontaneous bilateral renal hemorrhages accounted for only 3% of all case reports on spontaneous renal hemorrhage, and all cases were PAN [14]. Phillips, et al. [5], reported that Behcet's disease and segmental arterial mediolysis may cause spontaneous renal hemorrhage [4].

In our case, a CT scan revealed no sign of tumor or other causes of renal bleeding. Therefore, we strongly suspected PAN or another autoimmune vasculitis as the cause of spontaneous perirenal hemorrhage occurring consecutively. However, several serum immunologic markers related to autoimmune vasculitis were all negative except a slight elevation of the titers of ANA, anti-ssDNA, and anti-dsDNA antibodies. In addition, contrast-enhanced helical CT scan, angiography, and ^{67}Ga scintigraphy did not demonstrate any signs of severe inflammation, small aneurysm, arterial constriction, or occlusion. Needle or excisional renal biopsy or total nephrectomy was ideally necessary to understand vascular pathology for definitive diagnosis, but it was not feasible because the renal hemorrhage had been controlled by TAE and there was a risk for worsening renal function after renal biopsy.

The hypothesis that *Chlamydia pneumoniae* infection is an important pathophysiological mechanism in the development of arterial plaque rupture has been broadly accepted, and a long-term oral intake of macrolides (clarithromycin) is useful for the prophylactic management of acute coronary syndromes [15]. Although we had no reliable evidence to explain the precise reasons for spontaneous bilateral renal hemorrhages in our case, severe atherosclerosis was suspected to be closely associated with chronic infection with *Chlamydia pneumoniae* being the cause. CT angiogram clearly showed evidence of severe arteriosclerosis in conjunction with many plaque formations on the abdominal aorta, which may have influenced vascular vulnerability through prolonged vascular inflammation and finally caused bilateral spontaneous renal hemorrhages. Moreover, the patient received two types of antiplatelet (i.e., clopidogrel and aspirin) after percutaneous coronary intervention in the past. These facts may have contributed to the consecutive events of renal hemorrhage with a short interval.

Chronic infection has been also recognized as a risk factor for organ hemorrhage based on the cross-reactivity of the pathogen antigen and the infection-induced immune responses [16,17]. A case report that revealed a significant correlation between SAH and seropositivity for IgG/IgA antibodies against *Chlamydia pneumoniae* implied that subsequent infection of *Chlamydia pneumoniae* could be one of the risk factors for SAH from ruptured intracranial aneurysm [17]. Additionally, several studies have reported that *Chlamydia pneumoniae* infection is closely associated with acute exacerbation of chronic lung diseases, such as bronchial asthma, DPB, and COPD [18-20]. Furthermore, serum elevation of anti-*Chlamydia pneumoniae* IgA antibody is one of the circulating biomarkers of abdominal aortic aneurysm progression [21]. Hence, we speculated that chronic infection of *Chlamydia pneumoniae* might play an important role to induce long-term mild arteritis in both kidneys because the sensitivity of

^{67}Ga scintigraphy was not sufficiently high to detect a slight inflammation. As all indexes of anti-*Chlamydia pneumoniae* antibodies were elevated, we suspected chronic infection of *Chlamydia pneumoniae* may be influenced by bilateral spontaneous renal hemorrhages and right retinal artery occlusion. Therefore, we initiated oral administration of Clarithromycin (CAM, 400 mg/day, twice daily) for 198 days. However, all indexes of anti-*Chlamydia pneumoniae* antibodies were not significantly altered after a long-term CAM therapy (Figure 1D).

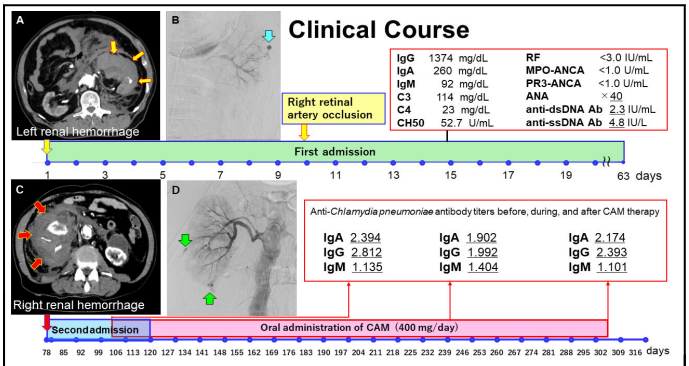

Figure 1: Clinical course, typical radiological findings, and immunological data within 316 days during and after two admissions. (A) The CT on the first admission (day 1) showed massive hemorrhage and extravasation of contrast media around the left kidney (yellow arrows). (B) TAE was immediately performed to stop bleeding from the upper branch of the left renal artery (blue arrow). Although vasculitis was highly suspected from renal hemorrhage and right retinal artery occlusion at day 10, all autoimmune markers were negative except a slight elevation of antinucleotide antibody (single- and double-strand deoxy nucleotide antibodies). The patient was discharged on day 63. (C) On day 78 from the first admission, the patient was again transported to the hospital owing to a massive hemorrhage of the right kidney (red arrow). (D) TAE was again performed to stop bleeding from the branch of the right renal artery (green arrows).

As all indexes of anti-*Chlamydia pneumoniae* antibodies were high, we suspected chronic infection of *Chlamydia pneumoniae* may be influenced by bilateral spontaneous renal hemorrhages and right retinal artery occlusion. Therefore, we initiated oral administration of Clarithromycin (CAM, 400 mg/day, twice daily) for 198 days. However, all indexes of anti-*Chlamydia pneumoniae* antibodies did not alter significantly during and after a long-term CAM therapy.

In addition, a case report demonstrated that systemic lupus erythematosus (SLE) or ANCA-associated vasculitis is involved in the mechanisms of spontaneous renal hemorrhage [22]. In our case, both Antinucleotide Antibody (ANA) and anti-ssDNA/dsDNA antibodies were slightly elevated, whereas neither MPO-ANCA nor PR3-ANCA was positive. These results indicate that autoimmune vasculitis could be concealed behind the backgrounds of spontaneous bilateral renal hemorrhages (Figures 2A- 2C).

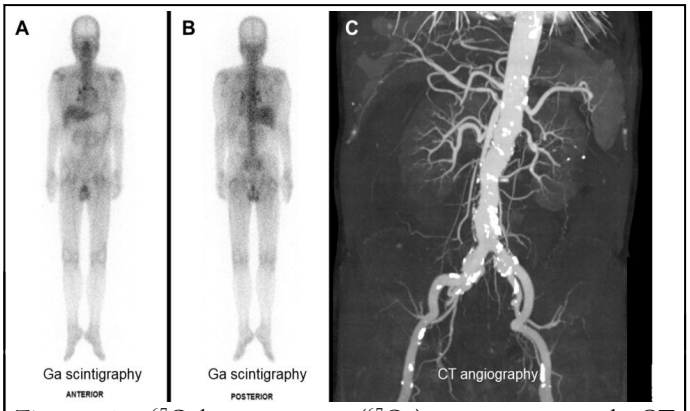

Figure 2: ^{67}Galium citrate (^{67}Ga) scintigram and CT angiograms during the first admission. (A,B) On day 114, anterior and posterior views of ^{67}Ga scintigram demonstrate no abnormal accumulation of ^{67}Ga, indicating the absence of severe inflammatory lesion or malignant tumor in the whole body. (C) However, a CT angiogram on day 98 reveals severe atherosclerosis and arterial plaques on the abdominal aorta and its branches. Calcifications are also observed in the left kidney.

There are some limitations for explaining the mechanism of spontaneous bilateral renal hemorrhages. First, the patient revealed no clinical symptoms of vasculitis due to SLE or other autoimmune diseases, such as PAN. Second, other immunological markers including C3, C4, CH50, and RF were all negative. Finally, a long-term CAM treatment did not alter the titer of anti-*Chlamydia pneumoniae* antibodies at all. Further examinations and careful clinical follow-up will be necessary to identify the real mechanism of spontaneous renal hemorrhage.

CONCLUSION

In conclusion, to our knowledge, this is the first case report of nontraumatic spontaneous bilateral renal hemorrhage with chronic *Chlamydia pneumoniae* infection. Severe atherosclerosis caused by chronic *Chlamydia pneumoniae* infection may predispose to the vascular vulnerability of the renal arteries in close associations with hypertension and oral intake of antiplatelets. Moreover, a slight elevation of ANA and anti-ssDNA/dsDNA antibodies suggests that underlying autoimmune vasculitis may finally pull a trigger to induce spontaneous bilateral renal hemorrhages although the real mechanisms remain unknown.

AUTHORS CONTRIBUTIONS

Ayaka Matsumoto, Yoshihiro Tanaka, Takero Terayama contributed to analyze the patient's clinical data and wrote the manuscript. Soichiro Seno, Yasumasa Sekine, Tetsuro Kiyozumi revised the manuscript critically for intellectual content. Daizoh Saitoh finally approved to be published.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The authors received the ethics approval and consent from the ethics committee of the hospital.

CONSENT FOR PUBLICATION

The authors received a written informed consent from the patient and his family for publishing his data as a medical case report.

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