CASE REPORT

Respiratory Bronchiolitis-Interstitial Lung Disease in Chronic Kidney Disease Mimicking Uremic Lung: A Case Report

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ABSTRACT

Introduction: Uremic lung is a frequent complication of chronic kidney disease (CKD), while interstitial lung is an inflammation of the parenchyma which impairs its capacity. These two conditions manifest similar radiological features with bilateral diffuse infiltrates. Therefore, their clinical appearance and radiological lesions are often mistaken.
Case: This study reported a case of a 55-year-old male patient with shortness of breath for 1 month and worsening 1 week before hospitalization. The patient had a smoking history for 30 years with severe Brinkman index, hypertension (HT), and diabetes mellitus (DM). Auscultation examination showed crackles in both lungs, while laboratory results showed anemia, leukocytosis, increased urea and creatinine levels, and radiological features of bilateral infiltrate suggesting a uremic lung. Furthermore, the ultrasonography showed bilateral chronic pyelonephritis and was diagnosed with CKD, uremic lung, pneumonia, anemia, hypoalbuminemia, mild hypokalemia, DM, and HT. The patient was treated with regular hemodialysis three times a week, and the serial chest X-ray after hemodialysis showed persistent bilateral infiltrates. An MSCT examination was also performed, and the results showed respiratory bronchiolitis-interstitial lung disease (RB-ILD). The patient was treated with antibiotic therapy, inhaled salbutamol, systemic steroids, and mucolytics. The patient was discharged from the hospital after the respiratory complaint were improved.
Conclusion: In uremia patients with bilateral infiltrates resembling uremic lung and unresponsive to hemodialysis or other therapies, interstitial illness should be explored. To improve patient management, risk factors for suspected interstitial lung disease should always be examined.

INTRODUCTION

Chronic kidney disease (CKD) is a condition which persists and gets worse with loss of kidney function and could develop into end-stage kidney disease requiring renal function replacement therapy such as dialysis to improve the patient's quality of life. Chronic kidney especially at the end-stage disease could influence almost any organ function. Respiratory system disorders are one of the most common complications of CKD, such as pulmonary edema, pleural effusion, acute respiratory distress syndrome, pulmonary fibrosis and calcification, pulmonary hypertension, hemosiderosis, pleural fibrosis, and obstructive sleep apnea are manifestations which appear in this stage. Loss of pulmonary function occurs directly due to the spreading uremia in the whole body and may be due to excessive fluid, anemia, immune worst, starvation, electrolyte disturbances, and acid-base disproportion.[1] However, evaluation of pulmonary

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function has not become a scheduled test in treating patients with CKD. The current state and clinical involvement of pulmonary complications in each individual with renal impairment are divergent, therefore, it is difficult to characterize properly. There are differences of pulmonary function on individuals hemodyalisis (HD) and it was showed that the restrictive disorders are the most common in these stages.[2] The explanation in the literature is still limited and could not reveal the entire relationship between these two conditions.[3]

Uremic lung is also a complication commonly seen in patients with CKD. However, with easy access to hemodialysis, its incidence decreases.[4] Based on National Health and Nutrition Examination Survey (NHANES) 2007-2012, the prevalence of pulmonary dysfunction in CKD patients of stages 1-4 reached a fairly high rate, with 10% restrictive lung and 16% obstructive pulmonary function.[5] This is due to the decrease in glomerular filtration rate in CKD or acute kidney injury (AKI) patients triggering the occurrence of pulmonary edema and respiratory muscle dysfunction as a result of fluid retention, metabolic and endocrine changes, as well as cardiovascular changes.[6] Patients commonly have dyspnea and radiological characteristics of "butterfly lung" or "bats-wing shadow". Meanwhile, pulmonary dysfunction and radiological abnormalities are generally reversible with hemodialysis.[7] Dialysis is primarily used to treat respiratory disorders in the uremic lungs.[8] It is a type of renal replacement therapy in patients with CKD or AKI because the kidneys play an essential role in blood-filtering to overcome excess fluid in the body and remove unwanted solutes and toxins. Therefore, dialysis therapy is a challenge in handling resistant uremia.[9]

The term interstitial lung disease (ILD) or diffuse parenchymal lung disease (DPLD) refers to several clinical disorders affecting the structures of the alveoli, interstitium, and small airways. Pulmonary manifestations are observed by a systemic process or affected organs. All ILDs have distinct clinical, radiological, and physiological features.[10] Furthermore, the Global Burden of Disease Study reported that interstitial lung dysfunction was the 40th most common death-related disease in 2013, with a mortality rate of 86% since 1990. The most common ILD, such as idiopathic pulmonary fibrosis, has a poor prognosis, with an average survival of 2-3 years after diagnosis. The prognosis depends on the underlying disease or a related condition for the other types.[11] Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) is a large group of DPLD, also known as ILD. It is a rare case with mild inflammatory lung disorder most commonly found exclusively in heavy smokers, usually 30 to 60 years of age and without a sex preference. Clinical symptoms are often non-specific; dyspnea on exertion and cough is non-productive for long.[12]

The relationship between chronic kidney and ILD has not been widely discussed in the literature. Therefore, this study presented the case of a patient with CKD with ILD resembling uremic lung.

CASE

The patient was a 55-year-old man complaining of shortness of breath for 1 month and worsening for 1 week. The tightness was mostly felt during activities, regardless of the weather or dust. Furthermore, a few months ago, the complaint was about dry cough but there was no phlegm and blood. The patient denied having chest pain but occasionally experienced discomfort and fatigue, nausea and vomiting, loss of smell, loss of taste, and no diarrhea. The patient had a history of smoking 1-2 packs daily for 30 years, with a severe Brinkmann index. For 3 months, the patient experienced swelling of both legs which became worse. The patient works as a civil servant. There is no history of pulmonary tuberculosis, asthma, and allergies. He has uncontrolled diabetes mellitus (DM) and hypertension (HT) for 17 years.

The physical examination on admission included blood pressure 197/100 mmHg, pulse 120x/minute, respiratory rate 29x/minute, temperature 36.5ºC, and oxygen saturation 94% using oxygen nasal cannula 2-3 l/i, weight 60kg, height 165cm, and BMI 22.03 kg/m^2. Chest examination showed the use of accessory breathing muscles, retraction of the intercostal muscles, and auscultation showed rhonchi in the lung fields. A cardiac examination revealed no additional heart sounds, while the blood test results were obtained on admission (Table 1). The patient has a urinalysis and was discovered to be glucose positive 3, ketone positive 3, hyaline cast positive, and bacteria positive. The patient was diagnosed with CKD stage 5, uremic lung, anemia, pneumonia, hypoalbuminemia, mild hypokalemia, type 2 DM, and HT stage II on admission. Furthermore, blood and urine culture test showed no bacterial growth. The spirometry test results were forced vital capacity (FVC) = 760 ml, forced expiratory volume 1 (FEV1) = 740 ml. The ratio between FEV1 and FVC (FEV1/FVC) = 970 ml, with the conclusion of very severe restriction. Bronchoscopy was not performed because the patient was often in an unstable condition.

Table 1. Laboratory results on admission and during treatment

Laboratory	On Admission	Day 10 of treatment	Day 15 of treatment	Day 20 of treatment	References
Hb	10.3	7.7	8.4	7.5	14.0 – 17.0 g/dl
Ht	31	22	24	22	45 – 56%
Erythrocytes	3.4	2.6	2.8	2.5	4.2- 5.40 ^{3}/mm ^{3}
Leukocytes	11.0	17.1	32.0	30.1	4.5 – 10,5. 10 ^{3}/mm ^{3}
Platelets	239	89	116	246	150 – 45.10 ^{3} / mm ^{3}
MCV	90	86	85	88	80 – 100 fL
MCH	30	30	30	30	27 -31 pg
MCHC	34	34	13,3	34	32 – 36%
RDW	15.0	13.8	11.9	14.0	11.5 – 14.5 %
Eosinophil	0	3	1	4	0-6 %
Basophil	0	0	1	1	0-2 %
Band Neutrophil	0	0	0	0	2-6 %
Segment neutrophil	95	77	88	79	50-70 %
Lymphocyte	4	9	3	8	20-40 %
Monocyte	1	11	7	8	2-7 %
Sodium			138	135	132-146 mmol/L
Potassium			4.10	3.40	3.7-5.4 mmol/L
Chloride			107	99	98-106 mmol /L
SGOT		18			< 35 U/I
SGPT		7			<45 U/I
GDS	264				<200 mg/dl
Ureum		105	78	84	13 – 43 mg/dl
Creatinine		3.10	4.10	4.64	0.67-1.17 mg/dl
PT	14.30		16.80	15.70	<11.50-15.50 second
APTT	32.90		36.00	35.60	26.00-37.00 second
D-dimmer	1840		2170	1210	<500 µg/L
Fibrinogen			358		250.0-365.0 mg/dl
Calcium	7.6		7.9	8.7	8.6 – 10.3 mmol/L
Albumin			2.90	2.49	3.5 – 5.2 g/d
Troponn T		0.05			<0.1 ng/mL
CK-MB		5			<16 u/L
Procalcitonin		38.00			<0.50 Ng/Ml

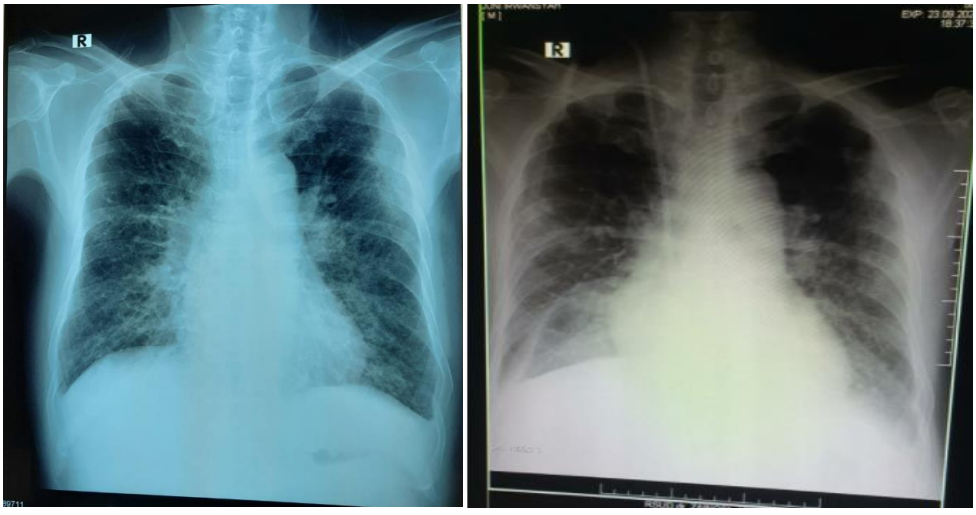

Figure 1. (a) Chest X-ray on admission (b) Chest X-ray after the third hemodialysis

The patient was treated with oxygenation using nasal cannula 3-4 l/i, 3 bags of packed red cell (PRC) transfusion, DM diet 1700 KKaL, Intravenous (iv) fluid Ringer Lactate 7 gtt/24 hours, Ampicillin sulbactam 3x1 gr iv, Omeprazole/24 hours iv, Furosemide 40 mg/12 hours iv, Methylprednisolone 62.5 mg/12 hours iv, insulin rapid acting 6-6-6 unit Subcutaneous (SC), insulin long acting 0-0-0-8 unit SC, recombinant human erythropoietin rh-Erythropoietin Alpha 300mg/iv (2x a week post hemodialysis), Zinc 1x20 mg angiotensin

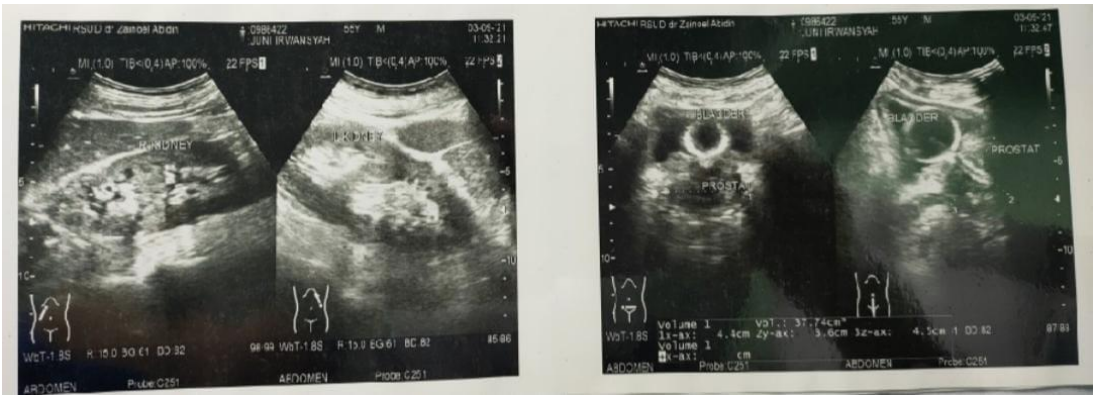

Figure 2. Abdominal ultrasonography

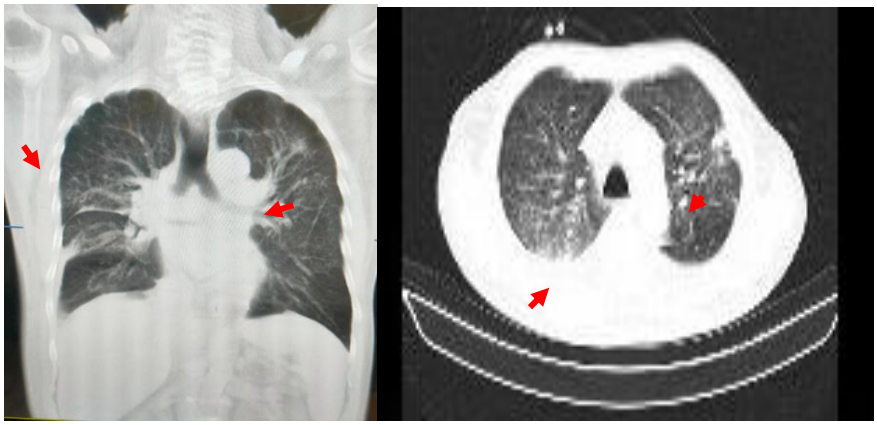

Figure 3. The red arrow indicates a bilateral ground-glass opacity with a faint micronodular centrilobular appearance and multiple lymphadenopathies.

receptor blocker (ARB) antihypertensive drugs once daily, hepatoprotector, angiotensin-converting enzyme (ACE) inhibitors HCL 1x10 mg, Adalat 1x30 mg, Atorvastatin 20 mg 1x1, Isosorbide Dinitrate 5 mg three times daily, N-Acetylcysteine 3x200mg, inhaled Ipratropium bromide, and salbutamol sulfate/12 hours. During the period of 1 month of treatment in the hospital, the patient received hemodialysis therapy 3 times, regularly 2 times a week. Clinically, the condition had improved, shortness of breath had reduced with oxygen saturation 93% room air, the patient was able to communicate, and eating and drinking were almost back to normal. Chest X-ray showed "bats-wing shadow" on admission (Figure 1).

The ultrasound results showed unclear cortical borders of the right and left renal sinus, suggesting bilateral chronic pyelonephritis (Figure 2).

A series of chest X-ray evaluations performed after hemodialysis showed that mottled cloudy spots were unevenly distributed around the periphery resembling ground-glass opacity in the left and right basal lung, and bilateral infiltrates persisted. Therefore, further investigation of suspected interstitial lung disease was performed. Although the diagnostic approach for ILD is more appropriate using high-resolution computed tomography (HRCT), multislice computed tomography (MSCT) can also assess lung function abnormalities which show widespread inflammation in ILD.[13]

DISCUSSION

CKD is a condition characterized by structural and functional abnormalities in the kidneys for at least 3 months due to a decrease in the glomerular filtration rate (GFR). The prevalence of CKD is estimated at 8 to 16% worldwide.[12,13] Decreased renal function in CKD patients also leads to decreased glomerular filtration and retention of uremic toxins or the substances which are no longer needed by the body, which under normal conditions will be metabolized and excreted through the kidneys.[14,15] Several molecules in the intermediate molecular range can affect the immune system, for example immunoglobulin light chain, neuropeptide Met-enkephalin and neuropeptide Y, endothelin-1, retinol-binding protein, adipokines resistin, and leptin. Furthermore, high-density lipoprotein in uremic patients

changes the protein profile and loses its anti-inflammatory properties. Post-translational modifications such as carbamoylation, oxidative modification, and advanced glycation products contribute greatly to uremic toxicity.[14]

Uremia is prone to affect the physiological work of various organs due to an increase in urea and creatinine, one of which causes pulmonary dysfunction.[2,14] Several mechanisms which lead to the uremic lung are increased pulmonary vascular permeability, chemokine, and leukocyte reactions from lung inflammation mediated by Interleukin-6 (IL-6), IL-8, IL-10, tumor necrosis factor (TNF)-α and neutrophil, endothelial injury, cellular apoptosis, oxidative stress, decreased hemoglobin levels, abnormal gas permeability, fluid overload, ventilation perfusion discrepancies, diminished oxygen supply due to hypoventilation, electrolyte imbalances, and metabolic acidosis.[16–18] Lung injury is one of the most common complications in patients with renal injury. The accumulation of uremic toxin will negatively affect lung gas exchange and lung mechanics. Excess fluid in the lung parenchyma can cause alveolar edema and metabolic acidosis leads to hyperventilation in the patient. Respiratory complications which include pulmonary edema and respiratory failure require the use of mechanical ventilation and a longer duration of mechanical ventilation. Epidemiological studies show that respiratory failure requiring mechanical ventilation is one of the major risk factors for mortality in patients with renal injury.[16,18] Pulmonary edema is the main cause of lung injury due to kidney disease which can be divided into hydrostatic and non-hydrostatic edema mechanisms. The main cause of hydrostatic edema is fluid overload which occurs due to decreased urine output and reduced cardiac output. Fluid overload greatly increases mortality in patients with complications of pulmonary injury, and restrictive fluid management can significantly improve lung function and shorten the duration of mechanical ventilation in these patients. Meanwhile, non-hydrostatic pulmonary edema occurs due to the absence of marked fluid overload. When the kidneys are damaged, the integrity of the alveolar-capillary barrier is compromised by systemic inflammation, uremia, and increased oxidative stress, leading to fluid accumulation in the lungs; this is often referred to as "nephrogenic pulmonary oedema". This condition cannot be significantly improved simply by resolving uremia and controlling fluid balance with dialysis due to the role of inflammatory mediators or increased levels of inflammatory cytokines, such as IL-6 and/or IL-8.[16]

The patient in this case has a long history of arterial HT with elevated blood urea and creatinine levels. The abdominal ultrasound imaging showed kidney damage with evidence of extensive and chronic glomerulonephritis. Furthermore, HT is one of the main risk factors for CKD.[19] Meanwhile, apart from being a risk factor, it also affects kidney disease.[20] Various studies discussed that an increase in blood pressure or HT increases kidney function damage.[21] This is because systemic HT transmits increased pressure in the intraglomerular capillaries, a sufficiently large increase in blood pressure can result in barotrauma and local vascular injury. The renal pathology that is usually observed in most individuals with HT is benign nephrosclerosis which is described as progressive aging of the renal vascular. Ischemic glomerular damage can occur but this condition is limited and progresses slowly over decades. Renal pathology in individuals with CKD is generally characterized by acute disruptive injury and fibrinoid necrosis of small arteries, arterioles, and glomerular capillaries, with prominent glomerular ischemia due to vascular injury.[19,21] Moreover, CKD results in increased blood pressure due to the major role of the kidney in regulating sodium and fluid homeostasis in the body. Changes in arterial pressure from as little as 1 to 3 mmHg have a major impact on kidney function and change the excretory system. Under normal circumstances, the body has an autoregulatory system, accurately balancing sodium and body fluids at various blood pressures. In CKD conditions, the autoregulatory mechanism for tubular reabsorption of sodium and fluids cannot work properly, resulting in retention and ending in an increase in blood pressure.[22]

Uremic lung has abnormalities in the radiological image and increased blood uremia and is known as pulmonary azotemia, pulmonary hyperemia with acidosis, uremic edema, fluid lung and has an indirect relationship with uremia as a result of severe glomerulonephritis and hemolytic-uremic syndrome. It is believed to occur due to the influence of uremia from any cause of etiology. Gutierrez, *et al*. reported a 23-year-old patient with uremia who had severe respiratory distress and renal impairment. Clinical and laboratory examinations yielded a diagnosis of advanced CKD accompanied by extensive infiltrate bilateral, further tests revealed more severe lung involvement leading to a diagnosis of uremic pneumonitis complicated by bronchopneumonia. This diagnosis is supported by tomography of the lungs and a state of severe uremic poisoning characteristic. Radiological findings showed an interstitial infiltrate spreading to both lung bases and an infiltrate spreading from the hilum with a characteristic of butterfly-like appearance. After repeated hemodialysis, pulmonary symptoms and alveolar progressive shortness of breath and bilateral leg edema.

Ultrasound results showed lung abnormalities in the form of pulmonary consolidation, pneumothorax, diffuse bilateral B line, and anechoic area above the diaphragm which showed pulmonary edema and pleural effusion. This condition occurred due to excess fluid in the alveoli, increased capillary permeability, and inflammatory reactions in the lungs. The patient was treated with intensive daily hemodialysis and showed significant improvement, his symptoms improved after five days. Subsequent therapy in the patient was changed to standard hemodialysis (3 times a week).[24]

Hemodialysis is the process of removing waste and extra water from the blood which the body no longer needs. Dialysis is an artificial replacement therapy for kidney function, especially in cases of CKD. Dialysis cannot completely replace lost kidney function, but to some extent it manages the elimination of body waste and oxidative stress by diffusion and ultrafiltration. The basic mechanism involved in the dialysis process is diffusion or the movement of solute particles across a semipermeable membrane (diffusion). Metabolic waste products which are not needed by the body, such as urea and creatinine, will diffuse down the concentration gradient from the circulation to the dialysate. The larger the particle size, the more difficult it will be to cross the membrane, hence waste substances which are not needed by the body will not re-enter the circulation.[25]

This case was accompanied by extensive glomerulonephritis of the right and left kidneys, causing an increase in severe uremia and affecting pulmonary dysfunction. Generally, after hemodialysis, there is a decrease in the urea levels and an improvement in pulmonary dysfunction. However, there was no improvement in lung function after hemodialysis, and serial chest X-rays showed bilateral diffuse reticulonodular infiltrates; therefore, further MSCT was performed, resulting in ground-glass opacity with faint micronodular centrilobular. There was fibrosis in segment 1, 2, 3 of the left lung with increased bronchovascular markings. Based on this description and accompanied by a history of smoking for 30 years with a severe Brinkman Index, the patient was diagnosed with RB-ILD, a condition of lung parenchymal abnormalities with diffuse inflammation which is often observed in heavy smokers.

Smoking is a major risk factor for this disease. Almost all patients with RB-ILD have a history of being an active smoker or ex-smoker, reaching 89% of all cases. The main clinical symptoms of this disease are shortness of breath alongside coughing and pulmonary function abnormalities, either restrictive or mixed type. The HRCT imaging in ILD showed centrilobular micronodules, ground-glass opacity, and peribronchiolar hilar thickening. Histological examination of RB-ILD patients generally shows accumulation of brown pigmented macrophages in the alveoli, accompanied by lymphocytic submucosal and peribronchiolar infiltrates and extensive perialveolar fibrosis. The diagnosis is generally made by a history of smoking, respiratory symptoms with an obstructive, restrictive, or mixed pattern on pulmonary function testing with reduced lung diffusion capacity, and characteristics of HRCT radiographic findings. A surgical biopsy or transbronchial biopsy is usually not required for diagnosis unless a definite diagnosis is difficult to establish.[26,27]

The patient was not only experiencing routine hemodialysis 3 times a week but also treated with inhaled salbutamol and systemic steroids during hospitalization. In cases of RB-ILD, smoking cessation or reduction is the mainstay of therapy and generally results in clinical stabilization of the patient or resolution of symptoms. The administration of oral corticosteroids is still controversial, and it is suspected that the clinical effect is only a temporary improvement.[28] Gradually, there was an improvement in the shortness of breath and blood urea levels during the time of discharge of the patient. Therefore, it is important for the clinicians to always consider this rare condition as part of the differential diagnosis when a chest radiographic diagnostic investigation reveals "butterfly lung" or "bats-wing shadows" in patients with renal failure.

CONSLUSION

It is important for the clinicians to always observe the possibility of a differential diagnosis on chest radiography with uremic lung. There are many things to consider in a uremic patient with a bilateral diffuse infiltrate. This case demonstrated RB-ILD in CKD unresponsive to hemodialysis.

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Conflict of Interest
The author stated there is no conflict of interest in this study.

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Authors' Contributions

Write manuscript, collect data of patient: BY, M, and DS. Review and revision: BY, M, DS, AS. All authors contributed and have approved the final version.

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