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Case Report

# Pulmonary Aspergillosis in a Patient with Membranous Nephropathy Treated with Rituximab and Cyclophosphamide: A Case Report and Literature Review

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## Abstract

Over the past decade, the management of membranous nephropathy (MN), a common cause of nephrotic syndrome predominantly affecting adults, has rapidly developed. Immunosuppressive therapies, including corticosteroids, alkylating agents (especially cyclophosphamide), and CD20-targeted therapies are widely used in the treatment of membranous nephropathy. Yet, as with many immunosuppressive agents, the major concern associated with its use remains the increased risk of infections. Aspergillus species are the most frequent cause of fungal infections of the lungs, of which invasive pulmonary aspergillosis (IPA) affects immunocompromised populations, which are increasing in number and diversity with the advent of immunosuppressive therapy for MN. We present a rare case of pulmonary aspergillosis in a patient undergoing rituximab and cyclophosphamide therapy for MN, aimed at alerting clinicians to the possibility of increased incidence and atypical presentation of pulmonary aspergillosis in these patients.

**Keywords:** Membranous Nephropathy; Immunosuppressive Therapy; Pulmonary Aspergillosis

## Introduction

Membranous nephropathy (MN) is a glomerular disease that can occur at all ages [1]. MN is a glomerular autoimmune disease and the most frequent cause of nephrotic syndrome in adults. About 80% of patients have unknown etiology (primary membranous nephropathy, PMN), and 20% are associated with other systemic diseases or exposures (secondary membranous nephropathy), such as systemic lupus erythematosus, hepatitis virus infection, or malignancy. In terms of disease prognosis, about one-third of patients have spontaneous remission. In patients at high risk of progression, immunosuppressive therapy with cyclophosphamide

and corticosteroid hormones significantly reduces the need for renal replacement therapy. Given the cancer risk, other treatments such as calcineurin inhibitors and CD20-targeted B cell depletion therapy (rituximab) have been developed [2].

## Case Report

A 63-year-old man was admitted to Peking University Third Hospital with edema of both lower limbs. On December 15, 2021, the patient developed concave edema of both lower extremities with no apparent cause, mainly on the left side, accompanied by elevated blood pressure, up to 190/100 mmHg. The test indicated urine protein +++, occult blood +-, D-dimer 1.15μg/ml, and serum creatinine 65μmol/L. No obvious thrombosis was found on ultrasound in the left lower limb, and local veins were widened. After treatment, blood pressure was reduced and controlled at about 150/100mmHg. After 1 month, 24h urinary protein measurement 6372(mg/24hr)↑; Urinary microalbumin/creatinine 4407 (mg/g.CRR)↑; Albumin-22 (g/L)↓ was performed on December 21, 2021, and the pathological results indicated stage I membranous nephropathy, lung CT indicated miliary nodules and T cell spot test of tuberculosis infection (TSPOT) positive, and irbesartan 150mg qd was given to control proteinuria, spirolactone, and hydrochlorothiazide qod diuretic swelling. Warfarin 1.5mg qd anticoagulant treatment improved after discharge. After discharge, the patient felt that his symptoms were alleviated and stopped taking the drug for 7-8 days. On February 21, 2022, the patient developed systemic edema accompanied by chest tightness without obvious inducement, which was persistent and could be relieved by sitting upright and supine position, aggravated after bent over, no sweating or discomfort in the precardiac area, etc., and was readmitted to the hospital for serum creatinine examination of 120mmol/L. Considering stage 2 acute kidney injury with nephrotic syndrome, rituximab 100mg was administered on February 23, 2022. On March 17, 2022, the treatment plan was adjusted to glucocorticoid and cyclophosphamide therapy. Cyclophosphamide 0.8g was given on March 19, 2022, the infusion process was smooth, and prednisone acetate 40mg qd was added orally. After 1 month, the patient felt that the urine volume decreased significantly, about 500ml/ day, and the foam in urine did not change significantly compared with before. The patient was given cyclophosphamide 0.2g qd intravenous infusion for 3 days from April 23, 2022, with a total infusion of 0.6g. The cumulative dose of cyclophosphamide for the patient is currently 1.4g. This time, the patient experienced more dyspnea than after exercise, accompanied by cough and dysphagia.

**Previous history:** The patient has a history of right hip replacement in 2018.

**Personal history:** Smoking more than 40 years, 30 cigarettes a day. Drinking for more than 40 years, about 400g a day. Have quit smoking and drinking for more than 1 year.

The patient was a middle-aged male with a chronic course of disease. The onset was edema of both lower limbs without obvious inducement. The diagnosis of membranous nephropathy was confirmed according to pathological findings considering nephrotic syndrome. The patient had received glucocorticoid, cyclophosphamide, and rituximab irregularly in the past, and belonged to the immunosuppressed population. The patient's chest X-ray before admission (a routine screening during the epidemic period of COVID-19 pneumonia) revealed multiple plaques in both lungs, with thin-walled cavity changes accompanied by right pleural effusion.

The possibility of infection was considered. In order to further clarify the nature and location of lung lesions, chest CT was further improved after admission, and the results showed multiple new cavities of different sizes, uneven thickness, and multiple spots in both lungs. In addition, the etiological examination results of the patient showed blood fungus B-1.3-D glucan detection (G test) >600(pg/mL) (strongly positive), IgG positive for aspergillus but galactomannan test (GM test) was negative. Further improve electronic bronchoscopy under local anesthesia, bronchoalveolar lavage in the lingual lobe of the left lung, injection of 60ml normal saline, recovery of 25ml clear liquid, positive GM test of bronchoalveolar lavage fluid, Next-generation sequencing (NGS) suggest Aspergillus tardus. The patient was treated with 400mg once loading of voriconazole and 200mg bid for maintenance, liver, and kidney function were monitored, and chest CT was re-examined after 3 months of antifungal treatment.

## Discussion

Membranous nephropathy (MN) is defined by a typical histopathological pattern of thickening of the glomerular capillary walls, gradual embedding of subepithelial immune deposits into the newly formed glomerular basement membrane, and immunofluorescence positivity of IgG and C3 particles [3, 4]. Although a kidney biopsy is an invasive procedure, it is still the gold standard for diagnosing MN [5]. Clinically, MN is associated with proteinuria, often (in approximately 80% of cases) in a nephrotic range (>3.5 g/d) [6]. Risk stratification in MN patients depends on proteinuria and creatinine (GFR) [7]. Glucocorticoids are widely used in the treatment of glomerular diseases due to their immunosuppressive, anti-inflammatory and podocyte protective effects [8]. Chemical agents, especially cyclophosphamide, are widely used to treat MN [9]. Cyclophosphamide (CTX) is the most commonly used cytotoxic drug in Asia, Europe, and the United States and is the only drug that has been shown to prevent kidney failure and death [10]. The modified Ponticelli regimen-CTX combined with methylprednisolone (MP) for 6 months every other month – is a treatment scheme recommended by KDIGO for the

treatment of IMN. In recent years, with the continuous discovery of anti-PLA2R and THSD7A antibodies, MN is believed to be related to the deposition of immune complexes on the epithelial side of the glomerular basement membrane by humoral immunity mediated by B lymphocytes [11]. Rituximab (RTX) is a chimeric mouse/human monoclonal antibody that induces B cell apoptosis and can treat MN by eliminating B cells. According to KDIGO guidelines, RTX should be considered in patients with severe nephrotic syndrome or those who do not respond to traditional immunosuppressive therapy. Rituximab has been shown to reduce proteinuria in MN patients and induce disease remission [7].

Aspergillus is ubiquitous in the environment, usually found in soil and decaying plants. In the spectrum of pulmonary aspergillosis, invasive pulmonary aspergillosis is the most serious entity. It is characterized by invasion of lung tissue by Aspergillus bacteria in most severely immunocompromised hosts. In addition, due to the rapid growth of mycelia, mycelia may invade the pulmonary artery, leading to avascular necrosis, intravascular thrombosis, and hemorrhagic pulmonary infarction [12]. The most common risk factors are long-term neutropenia, transplantation of hematopoietic stem cells or solid organs, inherited or acquired immunodeficiency, and the use of steroids or other immunosuppressants, including monoclonal antibodies and new small molecules for cancer treatment [13]. The patient in this case was an immunosuppressed person who had been using steroid hormones and other immunosuppressants, including cyclophosphamide and rituximab.

Invasive pulmonary aspergillosis (IPA) presents with very nonspecific symptoms, including dry cough, shortness of breath, chest pain, and hemoptysis. Fever may or may not be present, as most patients have low immunity and are unable to mount an adequate inflammatory response [14]. The main clinical symptoms of the patient in the case are dyspnea, especially after activity. The percentage of leukocytes, neutrophils, and C-reactive protein in the blood of this patient is not high, and there is also no sufficient evidence of inflammatory response.

The gold standard for diagnosis is by histopathological examination and surgical lung biopsy culture. However, patients with suspected invasive pulmonary aspergillus often have severe underlying disease, and therefore, surgical lung biopsies are usually not feasible. Sputum or bronchoalveolar lavage (BAL) fungal staining and culture are positive in about 30% of cases. Some non-invasive biochemical markers can also help to help diagnose invasive pulmonary aspergillosis, including serum and BAL fungal cell wall antigens, such as galactomannan (GM), beta-D-glucan, and aspergillus polymerase chain reaction (PCR). The performance of these biomarkers depends on reference cutoff values and the underlying host immune status. In comparison, the sensitivity and specificity of GM test and PCR of bronchoalveolar lavage solution were better than that of serum [15, 16]. If IPA occurs in patients who are not neutropenic, the fungal load in the lesion is lower, and the chance of the antigen appearing in the blood is lower [17]. Hence, serum GM is often negative in non-neutropenic patients. In this case, the GM test of the patient's serum was negative but the GM test of BAL was positive [18, 19]. NGS is an assay that can sequence the entire DNA/RNA of a sample, a process that does not require any primers or probes. It is expected to identify most pathogens. In addition, NGS can generate billions of DNA/RNA sequences per run, which enables metagenomic analysis [20]. Over the years, the cost of NGS has decreased, and it has become an attractive alternative method for discovering broad-based pathogens. With the advantages of being a broad spectrum, low time consumption, and high accuracy, the NGS method has made it easier to detect pathogens in patients with respiratory tract infection within 3 days [21]. Notably, in this case, according to NGS detection, the aspergillus in the BAL of the patient was not the common *Aspergillus fumigatus* but *Aspergillus tarda*. NGS can be an alternative diagnostic method or a complementary method to help clinicians make an appropriate decision. Radiographic images are also used to help diagnose invasive pulmonary aspergillosis; The preferred method is chest HRCT because it can identify the early stages of the disease, including nodules, consolidation lesions, and wedge-shaped infarcts. Invasive pulmonary aspergillosis should be treated with antifungal agents. Compared with amphotericin b, voriconazole has a higher survival rate, so voriconazole is chosen as a therapeutic agent to ensure the efficacy and safety of treatment [22]. The voriconazole treatment dose is 6 mg/Kg intravenously every 12 hours on day 1, then 3 mg/Kg every 12 hours thereafter. Patients can be transitioned from intravenous to oral medications once clinically stable at a dose of 200-300 mg every 12 hours [23]. Voriconazole is an inhibitor of CYP2C19 and CYP3A4, therefore, Monitoring should be performed based on the patient's response to therapy, the severity of illness, and if concerns for toxicity arise including transient visual disturbances, dose-related hepatotoxicity, skin rash, central and peripheral neurologic symptoms (often reversible), and cardiovascular Events [24, 25].

## Conclusion

With the wide application of immunosuppressants, pulmonary aspergillosis often occurs in immunocompromised people. The diagnosis of pulmonary aspergillosis in patients undergoing immunosuppressive therapy requires a high degree of clinical suspicion and awareness. Clinicians often rely on CT scans as well as biomarkers such as serology for diagnosis. NGS-based diagnostics can be especially important for hard-to-diagnose disease states when conventional diagnostic procedures fail.

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