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Case Presentation

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Pulmonary Cryptococcosis in a Patient with Membranous Nephropathy Treated with Rituximab: 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. While immunosuppression,

traditionally comprising alkylating agents with corticosteroids or calcineurin inhibitor-based regimens, has been the preferred therapeutic approach, randomized controlled trials utilizing the B-cell depleting agent, rituximab, have shifted its role to the forefront of MN therapy. Yet, as with many immunosuppressive agents, the major concern associated with its use remains the increased risk of infections. In particular, the risk of reactivation of tuberculosis and fungal infections has emerged as a significant infective complication of rituximab therapy. Cryptococcus infection, an opportunistic fungal infection, has been reported in patients undergoing rituximab treatment. We present a rare case of pulmonary cryptococcosis in a patient undergoing rituximab therapy for MN, aimed at alerting clinicians to the possibility of increased incidence and atypical presentation of pulmonary cryptococcosis in these patients.

Keywords: Membranous nephropathy; Rituximab; Cryptococcosis

Introduction

Membranous Nephropathy (MN) is a prevalent cause of nephrotic syndrome in adults and occurs less frequently in children **[1].** Nephrotic syndrome is observed in 80% of MN patients, characterized by heavy proteinuria, hypoalbuminemia, edema or anasarca, and hyperlipidemia, while the remaining cases are diagnosed earlier in the disease course upon incidental detection of proteinuria. The figure below **(Figure 1)** displays an updated algorithm based on the forthcoming revision of the KDIGO (Kidney Disease: Improving Global Outcomes) guideline for glomerulonephritis. This classification facilitates clinical decision-making regarding watchful waiting or immediate treatment with immunosuppression. Notably, Rituximab is also considered a first-line treatment for MN. However, due to its prolonged B-cell depletion, Rituximab carries an elevated risk of HBV and tuberculosis reactivation, along with other serious infections that have been reported.

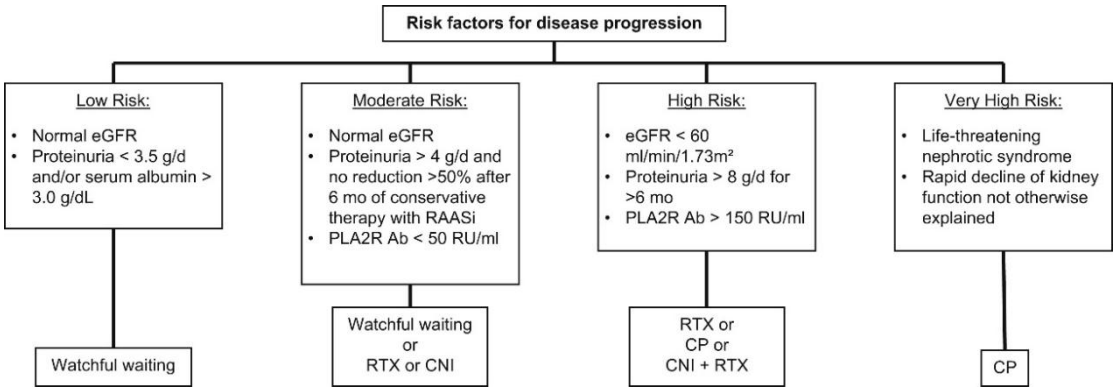


Figure 1: An updated algorithm based on the forthcoming revision of the KDIGO.

Case Presentation

A 63-year-old male presented to Peking University Third Hospital with intermittent edema of the lower limbs. The patient had initially developed edema of both feet 23 months prior (2020-06), which gradually progressed bilaterally. The edema was suffused and variable, with lighter symptoms observed in the morning and heavier symptoms in the evening. The patient also reported increased foam in urine and elevated blood pressure (140/100 mmHg), which worsened after physical activity, but without gross hematuria. Laboratory tests conducted at another hospital showed White Blood Cell count (WBC) of 4.79×10^9/L, Hemoglobin (HGB) of 138 g/L, Platelet Count (PLT) of 195×10^9/L, serum Albumin (ALB) of 24.7 g/L, serum Creatinine (Cr) of 79.8 umol/L, estimated Glomerular Filtration Rate (eGFR) of 91 mL/min/1.73m^2, 24-hour urinary protein quantity of 2.99 g/L, and PLA2R of 245.17 RU/mL. C reactive protein, immunoglobulin, complement, ANA, dsDNA, ENA, and ANCA showed no significant abnormalities. Renal puncture biopsy performed on December 8, 2020, revealed stage I membranous nephropathy. The patient was treated with cyclosporine 75 mg qd7+50 mg qd18 for six months. Subsequent examination showed significant improvement to bilateral lower extremity edema and an enhancement in 24-hour urinary protein fluctuation of 6.95-4.29 g/L. Kidney function evaluation results in April 2021 showed a serum creatinine of 126umol/L and 24-hour urinary protein quantity of 6.42 g/L. Despite two months of treatment with methylprednisolone tablets at 12 mg qd8 and repeated monitoring, no remarkable improvement was observed in urinary protein quantity, leading to a poor response to the "cyclosporine combined with glucocorticoid" treatment approach. After pulse treatment with methylprednisolone 24 mg qd8 + cyclophosphamide, ALB ranged from 19.3 to 24.5 g/L, Cr ranged from 93-109 umol/L, and 24-hour urinary protein fluctuated from 6.25-14.32 g/L. There was no

significant reduction in urinary protein quantity post-treatment. Treatment was adjusted in December 2021 to methylprednisolone 10 mg qd, causing urinary protein quantity to variate between 4.76-8.82 g/L in 24 hours. The patient presented to our hospital in March 2022, with methylprednisolone treatment reduced to 4 mg qd, and a single intravenous infusion of 500 mg rituximab administered on March 11, 2022. Following discharge, the patient developed genital herpes and was treated with external ointment and antiviral drugs (specific information is unclear). On April 7, 2022, an intravenous infusion of 100 mg rituximab was given, followed by the discontinuation of methylprednisolone on April 22, an additional intravenous infusion of 500 mg rituximab was administered on April 29, 2022, with a smooth process and no adverse reactions. One week prior to the patient's outpatient revisit to our hospital, edema of both lower extremities recurred. Following treatment with hydrochlorothiazide 25 mg qd and spironolactone 20 mg bid diuretics, the patient's edema showed significant improvement.

Previous history

The patient has a history of chronic pharyngitis lasting over 30 years, as well as hemorrhoids for more than 30 years. They have been diagnosed with hyperlipidemia for over 20 years and are currently receiving lipid-lowering treatment with atorvastatin 20 mg once nightly. Dry eye has been present for over 10 years. Hypertension has been diagnosed for over 1 year, with the highest recorded blood pressure being 160/100 mmHg. The patient is undergoing regular antihypertensive treatment with oral norhintal 50mg once daily, and they self-report blood pressure control within the range of 120-130/80-90 mmHg. One week ago, the antihypertensive treatment was adjusted to norhintal 100 mg once daily. Mild anemias, gallbladder polyposis, prostatic hyperplasia with calcification, and atherosclerosis of both lower limbs have been observed for the past 3 months.

Personal history

The patient has a smoking history of over 30 years, smoking 20 cigarettes per day, but has been smoke-free for more than 6 years.

The patient is a middle-aged male with a chronic disease course. Currently, the diagnosis of membranous nephropathy with nephrotic syndrome is definitive. In the past, the patient received irregular treatment with glucocorticoids, cyclosporine, and cyclophosphamide, experiencing repeated edema without significant improvement in urinary protein quantification. Therefore, the treatment effect was considered poor. Upon admission to our hospital in March 2022, the patient received

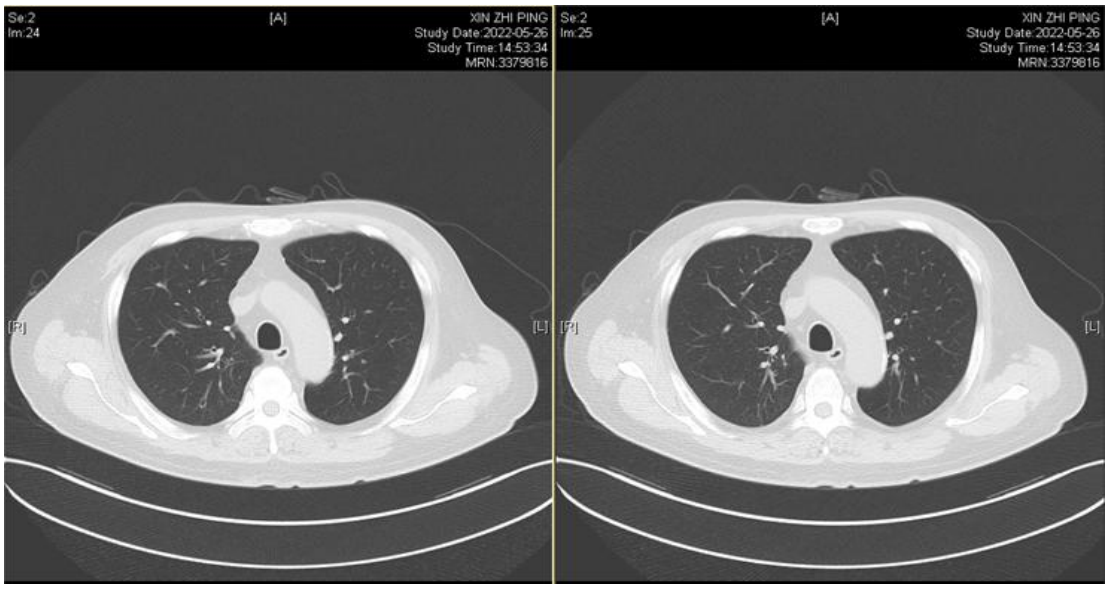
rituximab infusions: 500 mg on March 11, 2022, 100 mg on April 7, 2022, and 500 mg on April 29, 2022. However, there was no significant improvement in urinary protein quantity in the 24-hour period. Nevertheless, there was a progressive decrease in anti-phospholipase A2 receptor antibody levels (from 619.08 (RU/ml) to 270.802 (RU/ml)), and a progressive increase in blood albumin levels (from 15.2 (g/L) to 21.5 (g/L)).

After admission, the patient underwent relevant tests, yielding the following results: white blood cells 6.92(*10^9/L), red blood cells 3.37(*10^12/L), hemoglobin 97 (g/L), platelet count 323(*10^9/L); albumin 21.5 (g/L), serum creatinine 184 (μmol/L). Lymphocyte subsets absolute count: helper/inducer T lymphocytes absolute count 727.86 (/μl), suppressor/cytotoxic T lymphocytes absolute count 1271.02(/μl), B lymphocytes absolute count 0(/μl), CD4/CD8 ratio 0.57, B lymphocytes 0(%); 24-hour urinary protein quantity 3432.4 (mg/24hr). The quantitative measurement of anti-phospholipase A2 receptor antibody was 236.951 (RU/ml). Serum cryptococcus neoformans antigen test was positive. C-reactive protein and procalcitonin levels were within normal range. Blood EBV DNA and human cytomegalovirus DNA were negative.

The following factors should be taken into consideration: (1) Hypotension: The patient's dosage of nohintal was increased from 50 mg once daily orally to 100 mg once daily orally a week ago, and they have recently reported poor appetite and low blood pressure after admission. Given the potential risk of acute kidney injury due to inadequate intake and low blood pressure, the administration of nohintal should be discontinued, and regular monitoring of blood pressure and creatinine levels should be conducted. (2) Drug-related factors: The patient had a change in dosage of nohinol one week ago, and the possibility of drug-induced kidney injury should be considered, requiring continued monitoring. (3) Infection factors: Patients should be vigilant for infections when using immune preparations, and etiological tests need to be improved. The return of a positive cryptococcus neoformans antigen suggests the presence of an infection. The patient's follow-up medical history reveals no recent manifestations such as fever, cough, sputum, or hemoptysis. However, the infection status of the patient should be further assessed through chest CT.

The patient was a middle-aged to elderly male with a confirmed diagnosis of nephrotic syndrome. Hormones and CTX had been used by the patient for an extended period. Rituximab had been administered three times, leading to a state of immunosuppression. The patient exhibited symptoms of

cough, sputum, fatigue, and weight loss. The return of positive cryptococcus neoformans antigen was observed. Extensive questioning of the patient's medical history was conducted. The patient complained about the presence of a poultry farm near his previous residence, but he had moved away from that location over a year ago. The patient denied recent contact with pigeons and poultry. One year ago, the patient was admitted to another hospital due to a cough and yellow phlegm, and antibiotics were prescribed for suspected pulmonary infection (specific details are unknown). The chest CT scan revealed multiple nodules in both lungs, with solid nodules observed in the left lung near the pleura. Mesh-like shadows were also visible in both lungs. In conclusion, vigilance against pulmonary cryptococcus infection is warranted **(Figure 2).**



Note: Multiple nodules of varying sizes were observed dispersed throughout both lungs, with the larger one specifically identified in the left lung (Slice 2, Image 30). Additionally, a few fibrous shadows were scattered in both lungs, while the trachea and main bronchus appeared unobstructed. No enlarged lymph nodes were detected in the hilus and mediastinum. A small amount of pleural effusion was present on both sides, which was less compared to previous findings, and thickening of the pleura was observed bilaterally.

Figure 2: Chest CT image.

The reexamination of serum antigens for Cryptococcus neoformans still yielded positive results. A lumbar puncture was performed to obtain cerebrospinal fluid samples for further examination. No

significant abnormalities were detected in the cryptococcal examination of the cerebrospinal fluid. Additionally, cerebral MRI did not reveal any notable abnormalities. Therefore, disseminated cryptococcal infection of the central nervous system can be ruled out. Although no significant abnormalities were identified in the examination of cryptococcus in the bronchoalveolar lavage fluid, the patient was prescribed fluconazole at a dosage of 400 mg once and then 200 mg once daily intravenously. This treatment approach was based on the clear diagnosis of pulmonary cryptococcosis, the patient's symptoms, serological examination, and chest CT findings. A review of the chest CT was conducted one month later.

Discussion

Membranous nephropathy is characterized by the presence of subepithelial immune complex deposits that cause alterations in the glomerular basement membrane. The majority of membranous nephropathy cases are associated with antibodies targeting podocyte antigens, such as M-type Phospholipase A2 s (PLA2R1). Although the pathogenicity of anti-PLA2R1 antibodies has not been definitively proven, antibody titers tend to increase during clinical activity and decrease prior to clinical remission **[2,3].** Rituximab is a chimeric anti-CD20 antibody that induces B cell death through apoptosis **[4],** complement-mediated cytotoxicity **[5],** and antibody-dependent cytotoxicity **[6].** Multiple non-randomized studies have demonstrated that rituximab can achieve clinical remission in 60-80% of patients with primary membranous nephropathy **[7].** Pulmonary cryptococcosis is a deep fungal infection caused by Cryptococcus neoformans. This pathogen possesses a thick capsule that enhances its virulence and evades immune clearance within the body. Clinical and imaging manifestations of pulmonary cryptococcosis lack specificity, with most cases exhibiting either no symptoms or mild respiratory symptoms. Cough is the most common symptom, while fever, hemoptysis, chest pain, and chest tightness may also be present. Imaging findings typically fall into three categories: single or multiple nodular masses, lamellar infiltration, and diffuse mixed lesions. Given the patient's immunosuppressed status and the atypical clinical manifestations and signs, special attention should be paid to pulmonary cryptococcosis, particularly in relation to the development of cryptococcal meningitis **[8].**

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