CASE REPORT

A CASE OF SECONDARY MEMBRANOUS NEPHROPATHY DUE TO TUBERCULOSIS

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Membranous nephropathy is a common cause of proteinuria and nephrotic syndrome all over the world. It is classified as primary and secondary membranous nephropathy where primary disease formed around 70% of all the cases while the remaining cases could be secondary to autoimmune disease such as systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis and Sjogren's syndrome or solid organs tumours or drugs like NSAIDs and penicillamines and as our case today could be secondary to infective aetiologies such as Tuberculosis, Hepatitis B, C, HIV and Syphilis. In this writeup we present a case of secondary membranous nephropathy due to tuberculosis.

Keywords: Membranous nephropathy; Nephrotic Syndrome; Tuberculosis

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INTRODUCTION

We present a case of secondary membranous nephropathy due to Tuberculosis whereby we highlight the importance of a thorough investigation to look for secondary causes in a patient with membranous nephropathy as the treatment varies greatly. The tuberculosis was only discovered from imaging studies such as CT thorax as he did not have any obvious symptoms to suggest the infection. Following treatment with anti-tuberculous medication his proteinuria and renal function have improved.

CASE PRESENTATION

A 41-year-old Asian man with no prior medical history presented with weight loss of about 10 kg, non-bloody diarrhoea and some leg swelling for the past 2 weeks. He also complained of a dry cough with some skin itchiness. Otherwise, he did not have any melaena, altered bowel habits or haemoptysis. There was no significant family history.

Initial physical examination showed normal vital parameters with normal blood pressure. General examination revealed mild eye puffiness and bilateral ankle oedema without any noticeable skin rash. Cardiovascular, respiratory and abdominal examination were normal and unremarkable. There were no palpable lymph nodes. His diarrhoea was not concerning as it was more of a mild loose stool rather than increase in frequency and he was clinically overloaded and not dehydrated.

Blood investigation showed deranged renal function test with elevated urea and creatinine at 10.5 mmol/L and 333 umol/L respectively. The estimated glomerular filtration rate (eGFR) was only 17 ml/min/1.73m^2 (calculated using the CKD-EPI equation). There was no baseline kidney function test. Electrolytes were within normal range but calcium was slightly reduced at 2.11 mmol/L. Albumin was low at 31 g/L which continued to dip further. A complete blood count showed hypochromic microcytic anaemia with haemoglobin measuring at 99 g/L. An initial blood gas showed metabolic acidosis with a pH of 7.308 and bicarbonate levels of 16.1 mmol/L. Urine dipstick showed proteinuria of 3+ and hematuria of 2+. Urine albumin creatinine ratio (ACR) showed nephrotic range proteinuria measuring at 355.56 mg/mmol. Total cholesterol was also elevated at 5.9 mmol/L.

He was seen by the renal team and diagnosed with nephrotic syndrome with renal impairment at this point due to continuous drop in his albumin levels and nephrotic range proteinuria which the urine ACR result above showed more than 5g of proteinuria in 24 hours. Further investigations were sent to rule out secondary causes. Vasculitic screen were normal. Complements 3 and 4 were also within normal range. Myeloma screen was negative. Tumour markers and infective screening done were normal. Anti-phospholipase A2 receptor antibody (PLA2R) was also sent to rule out primary membranous nephropathy and it came back negative. An initial chest radiograph done did not show any abnormality. In view of the normal blood test, a CT Thorax, abdomen and pelvis were arranged to rule out any other causes. At this

point, he was discharged and managed as outpatient as his renal function remained static and he was clinically stable. The CT was done in late April 2022 and it revealed bilateral miliary nodular opacities throughout both lung fields with enlarged mediastinal lymph nodes. The findings showed distinctive 'tree-in-bud' appearances highly suggestive of Tuberculosis. (Figure 1) An upper and lower endoscopy were also arranged in view of the diarrhoea which did not show any anatomical abnormalities but duodenal biopsy revealed incidental finding of Giardiasis.

A renal biopsy was arranged and there were 18 glomeruli which 6 were globally sclerosed. There was diffusely abnormal marked thickening of the glomerular basement membrane and focal sclerosis were noted within some of the glomeruli. There were no vasculitic lesions or crescents. On silver staining there were prominent spikes in the basement membrane. Congo red for amyloid was negative. There was moderate chronic damage with 40% tubular atrophy and interstitial fibrosis. Mild interstitial inflammation was noted otherwise no tubulitis or granulomas. These changes were consistent with membranous nephropathy with 40% chronic damage. The renal diagnosis at this point was revised to likely membranous nephropathy secondary to Tuberculosis as his anti PLA2R antibody was negative.

He was referred to the pulmonologist due to the CT chest result and was diagnosed with Miliary Tuberculosis. Empirical anti-tuberculous medication was started in May 2022 after Multi-Disciplinary Team (MDT) meeting between the respiratory and renal team. A subsequent bronchoscopy done confirmed the diagnosis of Tuberculosis with positive TB-PCR result which is sensitive to both isoniazid and rifampicin. He was also started on furosemide and ACE-Inhibitors for symptomatic treatment of his oedema and proteinuria. He was given oral metronidazole to treat the Giardiasis. His renal function was monitored in the outpatient renal clinic which showed significant improvement following treatment with anti-tuberculous medication in May 2022 without the need of immunosuppression which further supported the diagnosis of Membranous Nephropathy likely secondary to Tuberculosis. (Table 1 and Figure 2)

His proteinuria and hypoalbuminemia have improved greatly following treatment however his renal function remained stable with an eGFR of 40 mL/min which he was diagnosed with CKD stage 3B secondary to membranous nephropathy.

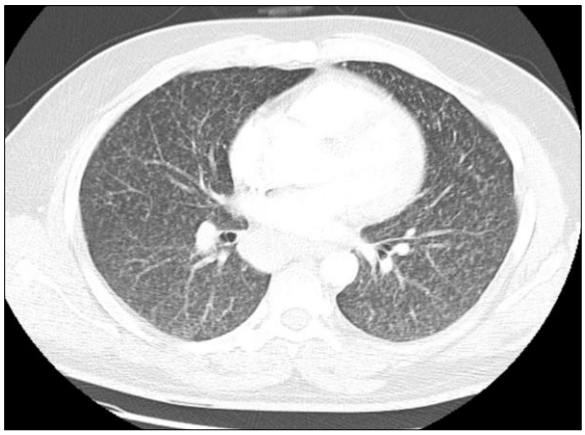

Figure-1: An axial view of CT thorax showing widespread miliary nodular opacities throughout both lungs.

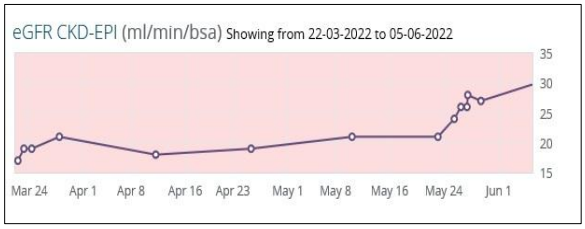

Figure-2: The improvement of eGFR during the course of treatment with anti-TB.

Table-1: The trend of creatinine during his follow-up

	23/3/2022	23/5/2022	25/5/2022	26/5/2022	6/6/2022
Urea (mmol/l)	10.5	15.1	11.9	10.6	8.3
Creatinine (umol/l)	**333**	**308**	**279**	**256**	**227**
Albumin (g/L)	31	27	24	22	24
Calcium (mmol/l)	2.11	2.16	2.30	2.23	-

DISCUSSION

Membranous nephropathy is well known to be the commonest cause of nephrotic syndrome in adult. Other causes of nephrotic syndrome in adult include focal and segmental glomerulosclerosis, minimal change disease, amyloidosis, lupus nephritis and diabetic nephropathy.[2] Membranous nephropathy is a histological diagnosis which could only be diagnosed with renal biopsy in the past but as renal medicine continues to advance, the uncovering of anti-phospholipase A2 receptor(anti-PLA2R) antibody has led to a change in which the guidelines now advocate the use of anti-PLA2R antibody to diagnose primary membranous nephropathy.[3] The causes of membranous nephropathy can be divided into primary and secondary. It is important to rule out secondary causes before making a diagnosis of primary

membranous nephropathy as the treatment of secondary membranous nephropathy involves treating the underlying cause while immunosuppressive therapies are used for primary disease. Example of causes that could lead to secondary membranous nephropathy are infection such as HIV, Hepatitis B and Hepatitis C, solid organ malignancy such as lung cancer, gastrointestinal cancer and prostate cancer, medication such as penicillamine, gold, anti-TNF (Tumour Necrosis Factor), immunotherapy and immunological condition such as systemic lupus erythematosus, rheumatoid arthritis and sarcoidosis.[4]

Although Tuberculosis is considered to be an infective cause, it is not a common infection that has been mentioned in literature to cause secondary membranous nephropathy. A few cases have been published over the years. A case published in Chinese Medical Journal in 2016 described a girl who had membranous nephropathy secondary to tuberculosis. Her proteinuria improved significantly following treatment with anti-tuberculous medication.[5] Another case published recently in India this year described a case of membranous nephropathy and tubulo-interstitial nephritis secondary to tuberculosis while a case from Japan described a case with lung adenocarcinoma and tuberculosis causing membranous nephropathy. Both of the cases had significant reduction of proteinuria following tuberculosis treatment.[6,7]

The clinical presentation for both primary and secondary membranous nephropathy are similar but the outcome and treatment are different. The outcome in secondary disease is often related to the original disease and the treatment is targeted to the original disease thus it is of paramount importance to differentiate between primary and secondary membranous nephropathy and the diagnosis should not depend merely on clinical presentation but it should also involve careful review and interpretation of the immunofluorescent findings in biopsy and serum antibodies.

Tuberculosis can affect various parts of the kidney including the glomerulus, tubules and interstitium. Renal involvement usually occurs in miliary TB due to haematogenic dissemination of the bacteria and renal biopsy may reveal findings such as caseating granulomas and in some patients, acid-fast bacilli can be found with Ziehl-Neelsen staining.[8] In our patient, the glomerulus was affected as evident by membranous nephropathic changes found on renal biopsy which were not explained by other causes. Tb also causes acute tubulointerstitial nephritis as demonstrated by a case reported in Japan and may cause papillitis which could lead to papillary necrosis.[9,10] Other than the kidney, tuberculosis also affects the ureter and bladder which may lead to ureteral strictures, dilatation and cystitis.

In conclusion, it is important to look for secondary cause in a patient with membranous nephropathy if primary disease has been ruled out as treatment differs greatly. Our patient demonstrated marked improvement in proteinuria and kidney function after treatment with anti-tuberculous medication.

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