



Case Report

Paraneoplastic Membranous Nephropathy in a Patient Diagnosed with Lung Carcinoma in Treatment Immunotherapy: A Case Report and Literature Review

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Abstract

Membranous nephropathy is the most frequent cause of nephrotic syndrome in adults, as well as the most common paraneoplastic syndrome associated with solid tumors. In these cases, it is essential to perform an adequate differential diagnosis since there are multiple causes of this syndrome.

We describe the case of a 77-year-old male who presented with heart failure in the context of a nephrotic syndrome with hyponatremia and proteinuria, and was finally diagnosed with locally advanced Squamous Cell Lung Carcinoma (SqNSCLC) (stage IIIB). Renal biopsy confirmed the diagnosis of membranous nephropathy, which in the clinical context of the patient and with the negativity of antiRFLPA2 antibodies was compatible with a nephrotic syndrome of paraneoplastic origin.

This was a patient with several comorbidities and poor pulmonary function, which limited the therapeutic options, so radical treatment with concomitant chemoradiotherapy and surgery were ruled out. Molecular analysis of the tumor showed a PD-L1 TPS of 20%, so authorization was requested for the use of first-line immunotherapy with Intravenous (IV) Pembrolizumab every 3 weeks off-label.

After initiation of immunotherapy treatment, there was evidence of improvement in the analytical parameters and clinical improvement to the point of resolution of the heart failure. In the first CAT scan evaluation, there was evidence of partial response of the disease, which was maintained until completing two years of treatment, with no evidence of progression until the last oncological consultation. Finally, the patient died due to an exacerbation of COPD while maintaining response of his oncologic disease.

Keywords: Lung carcinoma; Nephrotic syndrome; Paraneoplastic syndrome; Membranous nephropathy

Material and Methods

Description of a clinical case and literature review

Introduction

Nephrotic syndrome is a relatively frequent condition in clinical practice with a simple diagnosis based on pre-established criteria: Proteinuria > 3.5g/1.73 m² during 24 hours, hypoalbuminemia, edema and hyperlipidemia in the analysis. There are multiple etiologies, but in all the diseases with nephrotic syndrome, there is a defect in the glomerular filtration rate.

Membranous nephropathy is one of the causes of nephrotic syndrome, the most frequent in adults and much related to paraneoplastic syndromes secondary to solid tumors.

Etiopathologically it is based on a diffuse thickening of the glomerular basement membrane related to subepithelial electron-dense amorphous deposits, with progressive incorporation into the glomerular membrane, and which can be observed with silver staining as “herringbone” formations and with diagnostic pattern in immunofluorescence technique, that causes protein loss in the urine. Most of the times it has an idiopathic etiology, but it is important to make an adequate differential diagnosis since it is the most associated nephrotic syndrome with paraneoplastic syndromes.

The diagnosis is based on clinical history, remission of nephrotic syndrome if the oncologic disease responds to antineoplastic treatment and relapse of the same with recurrence of the oncologic disease since there is a physiological connection between the two pathologies.

Below we present a representative clinical case of a patient referred for clinical symptoms suggestive of heart failure in whom nephrotic syndrome was observed and after completing the studies, a diagnosis of primary pulmonary neoplasia was made.

Clinical Case

This is a 77-year-old patient at the time of diagnosis, with no known drug allergies, ex-smoker since 2009 (Smoking pack years, SPY 120) and with a history of arterial hypertension, dyslipidemia, paroxysmal atrial fibrillation, very severe Chronic Obstructive Pulmonary Disease (COPD) (Spirometry: FEV1 43%, Diffusion 24%), hypertensive heart disease and a Gleason 6 (3+3) prostate adenocarcinoma treated with radical radiotherapy in 2015. In treatment with Apixaban, Furosemide and Fluticasone/Vilanterol.

In March 2020, he went to the emergency department for progressive dyspnea, causing intolerance to decubitus and dyspnea at rest, in addition to edema in both lower limbs. Studies were completed with a diagnosis of nephrotic syndrome (sodium 122 mmol/L, total protein 5.5 g/dL, urine sodium 26 mmol/L, urinary

osmolarity 488 mOsm/kg, urine protein positive +++, total protein in urine 24h 528 mg/dL) and debut heart failure, so he was admitted to the Nephrology Department for diagnosis.

During his admission to the Nephrology Department from March to May 2020, complementary tests were performed and a percutaneous right renal biopsy was performed.

In the renal biopsy included for histopathological evaluation, the tissue was examined by light microscopy and immunofluorescence technique. The glomeruli preserved the architecture without thickened membranes, but with rigid luminal contours and without presence of spiculations or perforations in the staining with methenamine silver (Figure 1A, 1B). There was also no necrosis, sclerosis, amyloid deposition or crescents, acute tubular damage, crystals or calcifications. Direct immunofluorescence study showed intense pseudolinear deposits in the glomerular membrane of IgG (Figure 1C), C3 and kappa/lambda light chains (polyclonal pattern) (not shown). These findings are compatible with stage I membranous nephropathy (Deposits exclusively in subepithelial location).

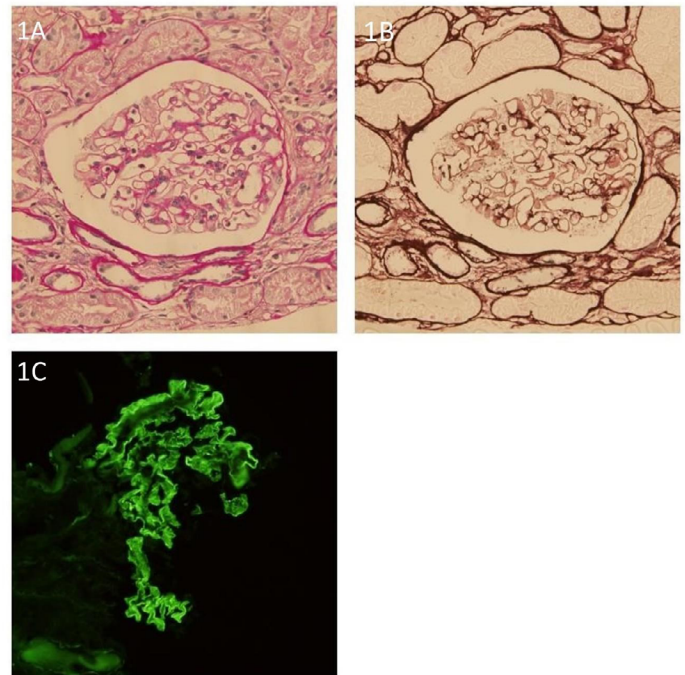


Figure 1: 1A. 400x PAS staining. Glomerulus with few intracapillary neutrophils and rigid capillary walls, without other significant pathologic abnormalities. 1B. Methenamine silver stain 400x. No spiculations or other alterations of the glomerulus are observed. 1C. Direct immunofluorescence study shows intense IgG deposits in the glomerular membrane, findings compatible with stage I membranous nephropathy.

Due to the history of pulmonary pathology and the negativity of antiRFLPA2 antibodies, the diagnosis was oriented towards a secondary nephrotic syndrome, so a thoracic CT scan was performed showing a right lung mass producing obstructive atelectasis over the middle lobe bronchi (cT2a). Fine Needle Puncture (FNA) of mediastinal adenopathy was performed by echo bronchoscopy with a diagnosis of Non-Small Cell Lung Carcinoma (NSCLC) morphologically compatible with an epidermoid carcinoma, EGFR wild-type, PD-L1 TPS 20%, ALK and ROS1 not translocated.

PET-CT was performed to complete staging, showing uptake in mediastinal nodes (cN2) confirmed by Endo Bronchial Ultra Sound (EBUS) and probable cN3 by prevascular adenopathy; therefore it would be a stage IIIB squamous cell carcinoma of the lung.

After evaluation, surgery was ruled out due to N3 involvement and radiotherapy because of extensive field and poor lung function by previous pathology (COPD with FEV1 43% and diffusion 24%). Evaluated in the medical oncology department, chemotherapy treatment with platinum combinations was discarded due to Performance Status (PS) ECOG 2 at the time of evaluation and multiple previous comorbidities. Following a special use request, first line treatment with Pembrolizumab IV 2mg/kg every 3 weeks (PD-L1 TPS 20%) was started in June 2020. The CT scan after three cycles showed a decrease in the mediastinal and subcarinal adenopathies, in the left para-aortic adenopathic conglomerate and in the primary tumor located in the middle lobe, findings compatible with a partial response, which is currently maintained (Figure 2).

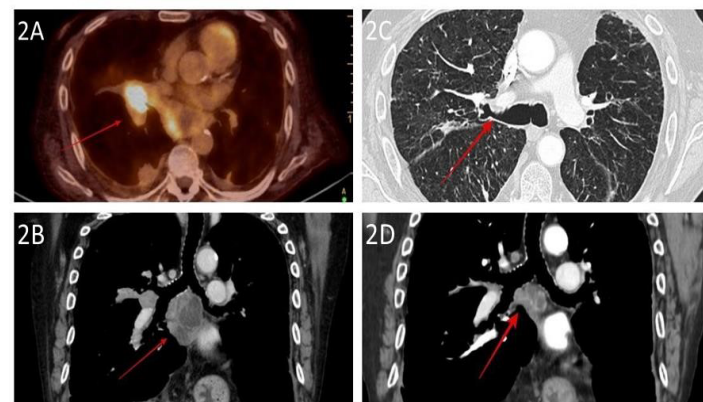


Figure 2: 2A-2B. Transverse PET and coronal CT at the time of diagnosis in April 2020. Mass is seen in the right hilar and subcarinal area. **2C-2D.** Transverse and coronal CT in maintained response in both locations in August 2022.

Control laboratory tests showed improvement of proteinuria and ionic alterations present before starting treatment with immunotherapy (sodium 137 mmol/L, total protein 6.2 g/dL, total protein in 24h urine 32.9 mg/dL). The patient presented marked improvement of the clinical manifestations compatible with heart failure with progressive decrease of dyspnea allowing him to lead an active life. The radiologic and analytical response was maintained after 19 cycles of treatment so he was followed up and received the last cycle of Pembrolizumab in August 2022. There was no data of progression until the last consultation in Oncology. He went to the Emergency Department in December 2022 for dyspnea and respiratory failure in the context of a respiratory infection and finally, the patient died due to an exacerbation of COPD unrelated to his baseline oncological disease.

Discussion

Nephrotic Syndrome (NS) is a group of clinical symptoms resulting from massive proteinuria caused by impairment of the glomerular filtration barrier [1]. The filtration barrier includes the glomerular basement membrane with endothelial cells lining its inner side and a monolayer of podocytes covering its outer aspect. In addition to being part of the glomerular filter, podocytes also regulate the synthesis of other components of the filtration barrier. Therefore, the integrity of these cells is crucial for maintaining normal ultrafiltration function.

Membranous nephropathy is an entity frequently associated with neoplastic diseases represented in clinical practice as a nephrotic syndrome [2,3]. It is important to perform an adequate differential diagnosis because the response of paraneoplastic nephrotic syndromes is usually associated with the response to antineoplastic treatment of the oncologic disease.

It has been described that complete surgical resection in patients diagnosed with lung carcinoma prevents the development or progression of nephrotic syndromes and decreases urinary protein loss, which significantly influences the quality of life of patients [4]. In the case of systemic treatments such as chemotherapy or targeted therapies, there are also studies that report regression of nephrotic syndrome if there is a systemic response to the neoplastic disease.

After reviewing the literature, there are cases reported in which there is evidence of improvement of nephrotic syndrome when a response of the oncologic disease is obtained after initiation of treatment. Yu et al describe the case of an 80-year-old patient diagnosed with advanced lung cancer and paraneoplastic nephrotic syndrome who achieved remission after treatment with radiotherapy and later showed resolution of the nephropathy [5].

Khan et al report a clinical case of a patient with triple negative breast cancer who presented a secondary paraneoplastic nephrotic syndrome, after treatment she presented complete pathologic response of the breast cancer that also resolved the nephrotic syndrome without recurrence of either pathology after 48 months of follow-up [6].

An interesting aspect of this clinical case is to highlight the treatment with immunotherapy. In the medical literature there are few published cases of patients with paraneoplastic nephrotic syndrome and treatment with immunotherapy, those described mainly refer to myasthenia gravis secondary to thymomas that can occur even after thymectomy and can be treated with immunotherapy [7,8].

Therefore, this case illustrates the importance of comprehensive management of the oncologic patient, being especially relevant the improvement of secondary clinical pictures after initiation of oncologic treatment for their baseline disease. In the case of a paraneoplastic nephrotic syndrome secondary to a tumor, its treatment would consist of the control of the oncologic disease without requiring specific treatment except for an adjustment of treatment to control the secondary symptoms of the tumor.

Author Contributions

María Mateos González: Writing – Original Draft Preparation, Editing, Conceptualization, Visualization. Luis León Mateos: Writing – Review & Editing, Supervision, Resources, Conceptualization. Beatriz Bernárdez Ferrán: Writing – Review & Editing. Elena Pintos Martínez: Resources, Review. Natalia Fernández Díaz: Editing. Nerea González García: Editing. Manuel Tourís Lores: Editing, Review. Rafael López López: Editing.

Conflicts of interest

María Mateos González: Travel, accommodations, expenses and registration to courses and congresses: Pierre-Fabre, Lilly, Novartis, Pfizer, Roche, Rovi, GSK, Leo Pharma, MSD, IPSEN Pharma, Sanofi, Pharmamar. Luis León Mateos: Travel, accommodations, expenses: Lilly, Novartis, Pfizer, Merck, Roche, and Bristol-Myers Squibb; honoraria for educational activities: Lilly, Novartis, Pfizer, Merck, Roche, and Bristol-Myers Squibb; honoraria for consultancies: Pharmamar, Bayer, and Pierre Fabre. Beatriz Bernárdez Ferrán: Travel, accommodations, expenses: Organon, Janssen, Roche, and Takeda; Honoraria for educational activities: Lilly, Abbvie, Organon, Astra-Zeneca, Pfizer, Merck, Roche, and Bristol-Myers Squibb; Honoraria for consultancies:

Merck, Pfizer, Pharmamar, Takeda, Daiichi Sankyo, Bayer, Astellas, Sanofi, and Novartis. Elena Pintos Martínez: No conflicts of interest. Natalia Fernández Díaz: Travel, accommodations, expenses and registration to courses and congresses: Sanofi, GSK, And ROVI. Nerea González García: Travel, accommodations, expenses and registration to courses and congresses: Sanofi, GSK, And ROVI. Manuel Tourís Lores: Honoraria for educational activities: Ipsen, Janssen, Astellas, Clovis, Bayer. Student grant support: Bayer, Glaxosmithkline. Travel support: Janssen. Rafael López López: Dr. Rafael López has received honoraria for participation in Advisory Boards from Roche, AstraZeneca, Merck, MSD, Bayer, BMS, Novartis, Janssen, Lilly, Pfizer and Leo; travel, accommodations and expenses from Pharmamar, Roche, BMS and Pierre Fabre; research funding from Roche and Merck; and is co-founder and shareholder in Nasasbiotech, Diversa Technologies.

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