CASE REPORT

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Paraneoplastic Cushing Syndrome and Membranous Glomerulonephritis Associated with Small Cell Lung Cancer

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ABSTRACT Small cell lung cancer (SCLC) comprises about 13% of all lung cancers. Ectopic Cushing syndrome is the second most common paraneoplastic entity following syndrome of inappropriate secretion of antidiuretic hormone in SCLC. Membranous nephropathy, is a pathological entity characterized by diffuse thickening in the glomerular basement membrane, as viewed under light microscopy. Solid tumors, including lung cancer, are preferentially associated with membranous glomerulonephropathy. In this case report, we will describe the process of diagnosis of SCLC and ectopic adrenocorticotropic hormone syndrome in a 79-year-old female patient who was followed-up for nephrotic syndrome and had a history of heavy smoking. Paraneoplastic syndromes can be attributed to other systemic diseases in elderly patients with many comorbid diseases. For this reason, they are usually diagnosed late and have a poor prognosis. With this case report, we aim to address this issue and create a broad perspective.

Keywords: Ectopic adrenocorticotropic hormone; ectopic Cushing; membranous glomerulonephritis; small cell lung cancer; paraneoplastic syndromes; hypokalemia

Paraneoplastic syndromes are rare disorders that are triggered by an altered immune system response to a neoplasm. They can be defined as non-metastatic systemic effects of neoplastic disease.[1]

Paraneoplastic syndromes are most commonly associated with lung cancer, reported in approximately 10% of cases.[2] Paraneoplastic syndromes associated with lung cancer can impair various organ functions. In addition to effects in most organs, it includes glomerulopathy and coagulopathy (Trousseau's syndrome) in both the arterial and venous systems.[3]

Small cell lung cancer (SCLC) accounts for 13% of all lung cancers.[4] Ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) is the second most common paraneoplastic entity after syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in SCLC.[5,6]

Membranous nephropathy (MN), is a pathological entity characterized by diffuse thickening in the glomerular basement membrane. Solid tumors, particularly lung cancer, are associated with membranous glomerulonephritis.[7]

The purpose of this case report is to increase the level of knowledge about rare diseases that have a causal relationship, and to enable them to be managed more easily for both the patient and the clinician by being diagnosed earlier.

CASE REPORT

A 79-year-old female patient with a history of 60 pack-years of smoking and hypertension for 8 years was diagnosed with MN by renal biopsy when nephrotic-range proteinuria (8 gr/day) was detected 7 months ago with bilateral ankle edema.

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TABLE 1: The patient's blood test results and normal reference ranges are presented in the table.

Laboratory parameters (Normal reference value)	Patient results
eGFR (mL/min, CKD-EPI)	76 mL/min
Venous blood analysis bicarbonate level (22-26 mmol/l)	41.8 mmol/L
Serum potassium (3.5-5 mEq/L)	2.2 mEq/L
Spot urine protein/creatinine ratio (g/d)	0.9 g/d
Serum adrenocorticotropic hormone level(9-52 ng/L)	354 ng/L
Morning serum cortisol level (4.8-19.5 µg/dL)	48.4 µg/dL
Dehydroepiandrosterone-sulfate level(12-154 µg/dL)	113 µg/dL
24-h urine free cortisol level (4-40 µg/24h)	5200 µg/24h
After 1 mg oral dexamethasone suppression test serum cortisol level(<1.8µg/dL)	32 µg/dL

eGFR: Estimated glomerular filtration rate;
CKD-EPI: Chronic kidney disease epidemiology collaboration.

At the time of diagnosis, she was examined for malignancy but no finding was found in favor of malignancy. Oral cyclophosphamide and methylprednisolone treatment was started. When she did not respond to cyclophosphamide treatment for 6 months, one course of rituximab was given. After this therapy, proteinuria was regressed to 1 gr/day. She was admitted to hospital with fatigue and general weakness, two weeks later. The initial blood pressure was 135/80 mmHg, the respiratuary rate 18 breaths per minute and the temperature was 36.5 °C. She was 165 centimeters and 84 kilograms. Abdominal obesity, moon face, plethora, a pad of fatty tissue between the shoulders and neck (buffalo hump), thin skin with bruises and stretch marks, pretibial edema and symmetrical proximal lower extremity muscle weakness were noted on physical examination. The facial swelling, moon face, and thin, hyperpigmented skin structure of our patient are shown in Figure 1. Laboratory results as shown in Table 1; severe hypokalemia with potassium level of 2.2 mEq/L (normal range 3.5-5) with metabolic alkalosis ph:7.57, normal range (7.35-7.45) and bicarbonate of 41.8 mmol/L (normal range: 22-26). Complete blood count, liver enzymes and liver function tests, serum creatinine and urea were at normal range.

The chest radiography showed mass-like lesions infiltrating upper and mid zone in right pulmonary lobe. As shown in Figure 2 contrast enhanced computed to-

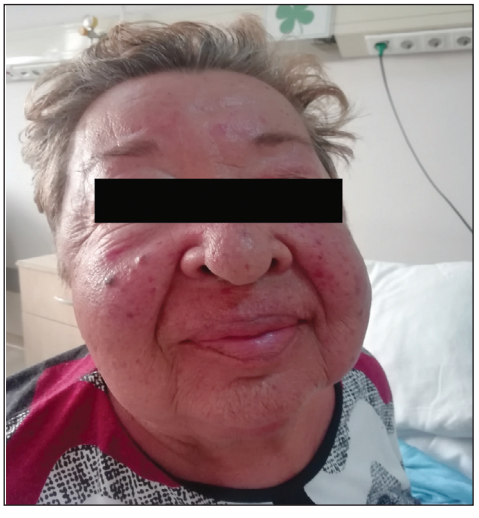

FIGURE 1: The facial pletorrhea, moon face and thin, hyperpigmented skin structure of our patient.

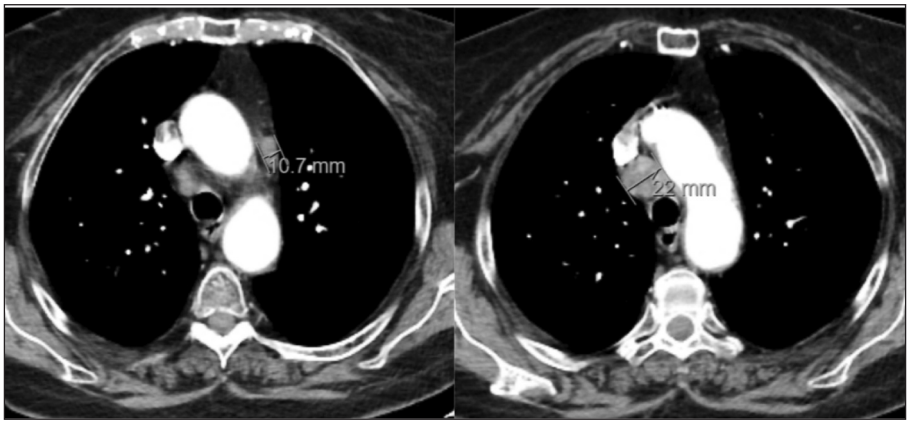

FIGURE 2: Contrast enhanced computed tomography of the thorax revealed multiple nodules (5-10 mm) suggesting malignancy in the superior segment of the lower lobe of the right lung and lateral segment of the left lingula, and lymph nodes (11-22 mm).

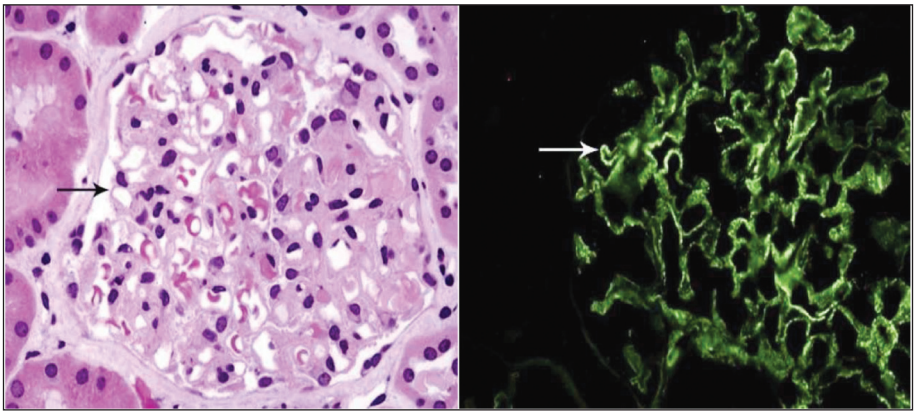

FIGURE 3: Renal biopsy. Thickening of the glomerular capillary basement membrane was demonstrated by routine H&E staining. Immunoglobulin G imunofluoresence shows diffuse granular deposits along the basement membrane in capillary loops (H&E stain, original magnification ×400).

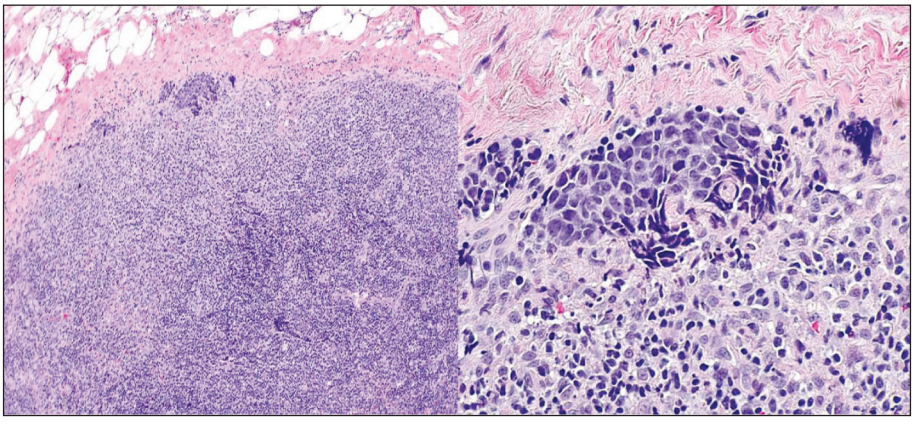

FIGURE 4: Mediastinal lymph node biopsy (H&E). Shown by hematoxylin-eosin staining. As a further examination, he was diagnosed with small cell lung cancer after positive staining with thyroid transcription factor-1 and chromogranin a was detected. Left side H&E Stain, original magnification x 100, right side H&E Stain, original magnification x 400.

mography of the thorax revealed multiple nodules (5-10 mm) suggesting malignancy in the superior segment of the lower lob of the right lung and the lateral segment of the lingula and lymph nodes (11-22 mm) that were thought to be metastatic in the mediastinum. Contrast enhanced computed tomography of the thorax revealed multiple nodules (5-10 mm) suggesting malignancy in the superior segment of the lower lobe of the right lung and lateral segment of the left lingula, and lymph nodes (11-22 mm) that were thought to be metastatic in the mediastinum. Positron emission tomography showed hipermetabolic lymph nodes at right lower paratracheal and preaortic regions, hypermetabolic mass lesion on left hilar region. In addition, both hepatic and bilateral adrenal metastatic lesions were revealed. Brain magnetic resonance imaging showed no cerebral metastasis and normal pituitary gland.

Cushing syndrome was suspected due to these findings. Serum ACTH level was 354 ng/L (normal range 9-52 ng/L), morning serum cortisol level was 48.4 µg/dL (normal range 4.8-19.5 µg/dL), dehydroepiandrosterone-sulfate level was 113 µg/dL (normal range 12-154 µg/dL), 24-h urine free cortisol level was 5200 µg/24h. We performed 1 mg oral dexamethasone suppression test and the level of serum cortisol was not suppressed. Plasma renin and aldosterone levels were at normal range. These findings were consistent with Cushing sydrome caused by ectopic ACTH production. She had already been diagnosed with membranous nephropathy with the kidney biopsy shown in Figure 3. We performed transbronchial mediastinal lymph node biopsy. As seen in Figure 4, the patient was diagnosed with SCLC. Octreotide and spironolactone were started because of

persistent hypokalemia despite oral and intravenous potassium replacement and to reduce cortisol levels before chemotherapy. Since metirapone and mifepristone were not available in our country, octreotide was given. Hypokalemia was not resolved after this interventions. Carboplatin and etoposide chemotherapy regimen was administered. The patient died on the 8th day of the first cycle of chemotherapy due to severe neutropenia-related infection. Informed consent was obtained from the son of the patient.

DISCUSSION

The frequency of paraneoplastic MN among membranous nephropathies has been found to be similar in most previous studies. Lee et al. reported that of 101 nephrotic syndromes, 11 were associated with malignacy and of these, 8 presented with MN.[8] In the study of Lefaucheur et al. on 240 patients with MN, cancer prevalence was determined at the rate of 10% in patients diagnosed with MN.[9] Advanced age (>65 years) and smoking history (>20 packs/year) are the guiding parameters in distinguishing malignant MN from idiopathic MN.[10]

Leafaucher et al. declared that carcinomas (83.3%) caused a large part of MN-associated tumors, and lung and prostate were the most common regions.[9]

Lung cancer is the leading malignancy associated with MN. SCLC accounts for about 13% of lung cancers.[8] Cushing syndrome cases associated with SCLC have been reported clinical Cushing sydrome that is seconder to ectopic ACTH secretion is uncommon, and is consistent with almost 3.2-4.5% of SCLC cases.[11] About 30% of SCLS cases are corresponding with EAS and is associated with poor prognosis.[2,3] The reasons of poor prognosis are advanced stage, worse response to chemotherapy, predisposition of severe infections and increased thromboembolic events in patients.[6,7] Due to these reasons, the average life expectancy varies between 3-6 months.[12,13] There are reports that systemic chemotherapy improves survival after lowering high cortisol levels.[14]

In order to decrease serum cortisol levels; glucocorticoid synthesis inhibitors such as ketoconazole, metirapone, etomidate, octreotide, mitotan or agents such as mifepristone may be used.[6] However, these treatments often fail to respond, and the average survival of the patients does not exceed one year.

Paraneoplastic syndromes are recognized later, due to their higher prevalence in advanced age and the accompanying comorbid diseases, and have a worse prognosis due to the aforementioned reasons. Each finding should be approached with suspicion, evaluated from a broad perspective, and all possible scenarios should be reviewed. If this approach is adopted, the diagnosis can be made in a shorter time and the effectiveness of the treatment can be increased.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Denis Çetin, Mustafa Murat Mıdık;* ***Design:*** *Denis Çetin;* ***Control/Supervision:*** *Mustafa Murat Mıdık;* ***Data Collection and/or Processing:*** *Denis Çetin, Mustafa Murat Mıdık;* ***Analysis and/or Interpretation:*** *Denis Çetin;* ***Literature Review:*** *Mustafa Murat Mıdık;* ***Writing the Article:*** *Mustafa Murat Mıdık, Denis Çetin;* ***Critical Review:*** *Denis Çetin;* ***References and Fundings:*** *Denis Çetin;* ***Materials:*** *Mustafa Murat Mıdık.*

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