10.5152/turkjnephrol.2019.3249

Case Report

Turkish Journal of Nephrology

Patient with Renal AA Amyloidosis Following Pulmonary Squamous Cell Carcinoma: A Case Report and Literature Review

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Abstract

A review of the literature revealed secondary amyloidosis (AA) associated with lung cancer in only 14 cases. With respect to the histological subtype, 8 of the cases were squamous cell carcinoma (SCC).Herein, we describe a patient with pulmonary SCC-associated AA. The patient presented with severe nephrotic syndrome 3 years after the diagnosis of malignancy and had no history of chronic inflammatory diseases. Our reason for evaluating these cases is that they are rare in the literature, and most are SCC-associated AA.

Keywords: Secondary amyloidosis, lung cancer, nephrotic syndrome, squamous cell carcinoma

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Received: 03.03.2018 **Accepted:** 06.04.2018

Presented in: This study was presented at the "34. National Nephrology, Hypertension, Dialysis and Transplantation Congress", "18-22 October 2017", "Antalya, Turkey".

Cite this article as: Tatar E, Taşlı F, Alpay H, Korkmaz A, Cayhan VK, Aktar M, et al. Patient with Renal AA Amyloidosis Following Pulmonary Squamous Cell Carcinoma: A Case Report and Literature Review. Turk J Nephrol 2019; 28(3): 225-8.

INTRODUCTION

Secondary amyloidosis (AA) is a disorder often associated with chronic inflammatory disease (i.e., familial Mediterranean fever; FMF). AA is caused by systemic extracellular accumulation of serum amyloid fibrils, primarily in the renal tissue (1, 2). The association of amyloidosis AA with solid organ tumors is quite rare. It most commonly accompanies renal cell carcinoma (3). AA has been described in a few patients with primary lung tumor (4-7). In the majority of these cases, histologic subtyping of the primary tumor has not been clearly elucidated, but rather classified under "non-small cell lung carcinoma" (4, 6).

Globally, lung cancer is the leading cause of death due to malignant diseases contributing to 17.6% of total carcinoma deaths (8). Today, it is notable that both the incidence of malignancy and/or cancer treatment-related renal diseases and the risk of carcinoma development in patients with nephrotic syndrome are increasing (9, 10). Indeed, the association between membranous glomerulonephritis (MGN) and carcinoma is not considered a coincidence, but a classic paraneoplastic syndrome. Of the MGN, 10% are paraneoplastic, and the lung cancer is the leading tumor type (9). Additionally, in a population-based cohort study in Denmark; patients with nephrotic syndrome have demonstrated an increased risk of carcinoma of 73% (most often lung and kidney carcinoma) when compared to general population (10).

In the literature, the association of lung cancer with AA has been reported in only 14 cases. With respect to the histological subtype, squamous cell carcinoma (SCC) constituted 8 of them. Herein, we report a case of a severe nephrotic syndrome due to AA associated with SCC of the lung. In addition, we evaluate pulmonary SCC-induced amyloidosis AA cases in the literature.

CASE PRESENTATION

A 67-year-old male was admitted to our outpatient clinic with extensive generalized edema, malnutrition, and shortness of breath that lasted for 3 months. He was hospitalized upon detection of kidney failure accompanied by severe nephrotic syndrome. Three years prior to admission, he was diagnosed with pulmonary SCC (stage 3a-T2aN2M0) and treated nonsurgically.

Transbronchial fine-needle aspiration cytology (FNAC) with the sampling of mediastinal lymph nodes was used to diagnose the primary pulmonary lesion and classifying the specific tumor type. The tumor had features of clustered polygonal cells with hyperchromatic nuclei, orangeophilic cytoplasm on the Pap stain, demonstrating keratinization and necrotic background. Immunohistochemistry (IHC) staining to identify p63 and the high-molecular weight cytokeratin positivity was unavailable.

At the time of cancer diagnosis, he received six cycles of cisplatin/gemcitabine followed by radiotherapy. At the 2nd year follow-up, metastasis to the opposite lung was detected on the positron emission tomography-computed tomography (PET-CT), and the patient received four cycles of carboplatin and docetaxel therapy. The last adjuvant chemotherapy was given 6 months before. From the cancer diagnosis to the last follow-up, the patient had no evidence of renal failure and hematuria or proteinuria. In addition, PET-CT examinations did not indicate any tumor or a lesion in the kidneys.

Laboratory data and blood chemistry included albumin 1.5 g/dL, blood urea 31.0 mg/dL, creatinine 1.4 mg/dL, eGFR:52 mL/min/1.72m^2, total cholesterol 456 mg/dL, triglyceride 571 mg/dL, quantitative proteinuria 11 gm/d, C-reactive protein 54.0 mg/dL (normal range, 0-5.0 mg/dL), serum amyloid A (SAA) 34 mg/L (normal range, 0-6.4). Urinalysis revealed 3+ proteinuria and no hematuria.

The patient underwent renal biopsy. Immunofluorescence microscopy showed no specific features. On hematoxylin- and eosin-stained tissue sections, there was eosinophilic material in 21 glomeruli, arterioles, and interstitium, which were also weakly stained with PAS. The Congo red study demonstrated capillary wall staining with global and segmental staining of amorphous deposits in 3 and 18 glomeruli, respectively. In addition, IHC detected AA type of amyloid in the specimen (Figure 1).

The FMF gene mutation analysis of the patient was negative, and no monoclonal gammopathy was detected in protein and immunofixation electrophoresis.

The patient had no history of chronic inflammatory arthritis, chronic sepsis, tuberculosis, periodic fever syndromes (FMF), and Crohn's disease. Thus, AA was associated with SCC of the lung. The patient had the ECOG Performance Status III, which impeded any further treatment, and he was discharged with the maintenance of best supportive care. Informed consent was obtained from all participants included in the study.

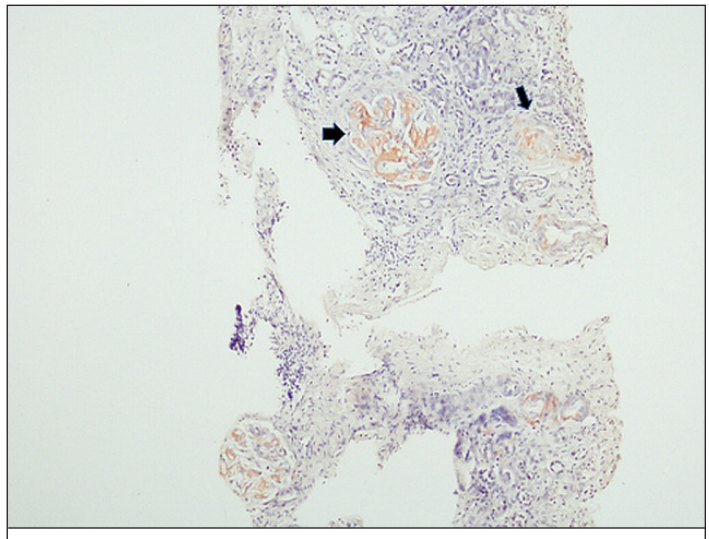

Figure 1. Amyloid Deposition in Glomeruli and Vessels (Congo Red; x100)

DISCUSSION

In literature, the association of primary lung tumors and AA is extremely rare, and the number of cases reported to date is 14. Of these, 9 cases were classified as non-small cell lung carcinoma. However, the pathological subtyping of this group disclosed the SCC histology in 8 of them (8/9). In particular, the association of AA with SCC of the lung is noteworthy; however, it is not yet certain whether it is a coincidence or a pathogenetic mechanism by which we can derive a causal relationship. To specify the frequency of the AA deposition in SCC, Ueno et al. (11) examined 266 specimens of SCC or dysplasia in the oral cavity, pharynx, and larynx and identified amyloid deposition in 11%, 36.4%, and 59.5% in the squamous cell lesions of the oral cavity, pharynx, and larynx, respectively. These findings highlight the increased predisposition of amyloid accumulation particularly in SCC of the distal portions of upper respiratory tract (11). In this study, the association of AA with all SCCs was 29%, and AA overexpression was found to be higher in SCC cases compared to dysplasia (40% vs. 59.5%, respectively). Among the anticytokeratin monoclonal antibodies, CK1 and CK14 reacted with 100% and 44.4% of the amyloid deposits of SCC, suggesting that SCC-associated AA may originate from cytokeratins in cancer cells. Similarly, 4 of the 8 cases (SCC of the lung with AA) mentioned above had the AA overexpression in the lung tissue, and 3 of them had a lethal course and were described in the necropsy study.

In another study, Oz Atalay et al. (12) investigated the clinic pathological behavior of AA in renal cell carcinoma (RCC) patients and reported the overexpression of AA in high-grade tumors. These RCC cases with increased immunoexpression of AA had had a very poor survival (12). In the light of this information, the association of pulmonary SCC with AA overexpression may be a poor prognostic indicator. There is a need for large-scale work in this area.

Including our patient, there are 3 cases described in the literature admitted with AA months and/or years after the diagnosis

Table 1. Biopsy-proven AA associated with squamous cell carcinoma of the lung

No	Author, (year)	Age (year)/ Sex	Diagnostic Method/Involved Organ(s)	Local/Generalized Disease AA Overexpression	Time to Detection of AA Following Cancer Diagnosis	Outcome
1	Kimball et al. (1961)	?	Autopsy series/necropsi	Generalized AA	Unknown	Died
2	Melato et al. (1981)	?	Autopsy series/necropsi (lung)	Local AA	Unknown	Died
3	Meyrier et al. (1985)	59/M	Case report/kidney biopsy	Generalized AA	1 year before	Died
4	Focan et al. (1985)	70/M	Case report/necropsi(gastrointestinal tract and bone marrow)	Generalized AA	Unknown	Died
5	Richmond et al. (1990)	72/M	Case report/necropsi (lung, kidney, bowel, adrenal glands, liver, spleen, portal vein, and pancreatic vessels)	Local and generalized AA	Simultaneously	Died
6	Garthwaite et al. (2003)	64/M	Case report/lung and kidney biopsy	Local and generalized AA	Unknown	Alive
7	Barceló et al. (2003)	33/M	Case report/rectal biopsy	Generalized AA	20 days	Died
8	Gueutin et al. (2013)	56/M	Case report/kidney biopsy	Generalized AA	1 year before	Alive
9	Our case	67/M	Case report/kidney biopsy	Generalized AA	3 years before	Alive

of malignancy (5, 7). Almost all had systemic organ involvement, mainly the kidney. In some cases, the presence of AA in the pulmonary tissue has suggested that SCC-induced serum amyloid A may be responsible for the process (13). Serum amyloid A is an inflammation-induced acute phase reactant released by cytokines. Serum AA levels have been associated with the clinical stage and progression of various cancers, such as hepatocellular, ovarian, renal, uterine, nasopharyngeal, and lung carcinoma (13). In the meta-analyzes of Biaoxue et al. (14) (9 trials, 1392 cases) for lung cancer, SAA levels were shown to be higher than healthy individuals and associated with disease progression. Furthermore, when lung cancer subtypes are evaluated, the SAA increase in SCC is significantly higher than the other carcinomas. In conclusion, SAA may both have a diagnostic and prognostic value in SCC of the lung and may be an important factor leading to the development of the AA type in these cases. The characteristics of our patient and other cases in the literature are presented in Table 1.

CONCLUSION

As a result, the AA type is more common in the SCC type lung carcinoma. At the time of the SCC diagnosis, local AA overexpression in the lung biopsy is a poor prognostic indicator. SCC-associated high SAA levels may be responsible for AA type amyloidosis with systemic organ involvement, and these patients often present with nephrotic syndrome. Further work is needed to clarify this issue.

Informed Consent: Informed consent was obtained from all participants included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.T., H.A., A.A.; Design - E.T.; Supervision - A.A., E.T.; Resource - E.T., F.T., A.A.; Materials- E.T., F.T., H.A., A.K., V.K.C., M.A., N.K., M.K., A.A.; Data Collection and/or Processing - F.T., H.A., A.K., V.K.C., M.A., N.K., M.K.; Analysis and/or Interpretation - E.T., A.A.; Literature Search - E.T., F.T., A.A.; Writing - E.T., A.A.; Critical Reviews - E.T., F.T., A.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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