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Original Paper

Microalbuminuria in Patients with Lung Cancer

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In a prospective study of 102 outpatients with histologically proven lung cancer, the prevalence and prognostic significance of microalbuminuria (urinary albumin excretion > 20 μg/min) were analysed. 65 consecutive outpatients with benign lung disorders served as controls. An immunoturbidimetric assay, sensitive at low concentrations, was used to quantify the albumin excretion rate in timed overnight urine samples. Patients with malignancies had a significantly higher frequency of microalbuminuria (32.4% compared with controls, 13.8%, $P < 0.01$) and median urinary albumin excretion rate (13.4 versus controls, 8.9 μg/min, $P < 0.003$). Urinary albumin excretion was significantly higher in lung cancer patients with TNM stage III and IV. Patients with malignancies and microalbuminuria had a significantly lower survival rate than patients with normoalbuminuria (probability of survival 1 and 3 years after diagnosis 66% and 16% versus controls, 22% and 4%, $P < 0.00001$). In a multivariate model, which adjusted for age, sex, performance status, histological type and TNM stage, microalbuminuria continued to be a significant predictor of survival. In conclusion, an increased prevalence of microalbuminuria has been demonstrated in patients with lung cancer. The presence of microalbuminuria was associated with advanced disease stage and poor survival. © **1998 Elsevier Science Ltd.**

Key words: microalbuminuria, albuminuria, urine, prevalence, survival, lung neoplasms
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INTRODUCTION

SLIGHTLY AND persistently elevated urinary albumin excretion is a well-established risk factor in many disorders. The presence of microalbuminuria indicates an increased risk of developing end-stage renal disease and non-renal vascular complications in diabetes mellitus [1, 2]. Microalbuminuria also seems to be predictive of morbidity and mortality in non-diabetic subjects [3, 4]. Recent studies have suggested that urinary albumin excretion is influenced by malignancies [5–7]. Hypothetically, microalbuminuria may be a non-specific marker of malignancy reflecting a microvascular response to tumour-related mediators [5, 8]. Furthermore, microalbuminuria may have prognostic significance in malignancies, with presumed urinary albumin excretion reflecting the severity of the disease and response to treatment [6, 9].

Paraneoplastic glomerulopathies have been associated with different malignancies [10, 11]. A high prevalence of proteinuria has been demonstrated in patients with a variety of malignant diseases [5–7]. Survival of patients with malignancies seems to be substantially reduced in the presence of proteinuria [5, 6]. However, the link between increased urinary protein excretion and malignancy remains to be elucidated and information on urinary albumin excretion in patients with malignant diseases using sensitive assays is lacking. In the present study, we report the prevalence and prognostic significance of increased urinary albumin excretion in patients with lung cancer.

PATIENTS AND METHODS

Between May 1993 and June 1994, patients suspected of having a malignant lung disease attending the Department of Pulmonary Medicine, Gentofte University Hospital, Copenhagen, were included in the study. The study population comprised 177 consecutive patients admitted for the first time for the diagnosis of pulmonary lesions on chest X-ray. Histologically confirmed malignant diagnoses were obtained in 112 patients. 2 patients with mesothelioma and 8 patients with metastases from malignancies other than primary lung cancer were excluded. 65 patients had benign pulmonary

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disorders and were used as controls. 22 patients with diabetes mellitus ($n = 6$), hypertension ($n = 5$), renal disease ($n = 2$), treatment with nephrotoxic drugs ($n = 1$), hypercalcaemia ($n = 1$), hyperuricaemia ($n = 1$) and patients with a positive urinary dipstick test for leucocytes and nitrites ($n = 6$) were not included. A malignant diagnosis was obtained in 13 (59%) of these patients. No patient had a history of previous malignancies or had been treated with chemotherapy or radiation therapy. Furthermore, no patient had metastatic invasion of renal tissue or retroperitonal lymph nodes with hydronephrosis.

Histopathological tumour diagnoses were classified according to WHO [12]. Each patient with primary lung cancer was staged according to the TNM system [13]. Clinical staging included chest radiography, CT-scan of the thorax and, in some cases, of the abdomen and brain, fiberoptic bronchoscopy or percutaneous transthoracic needle biopsy, mediastinoscopy, cytological examination of pleural fluid, and in small cell carcinoma bilateral bone marrow biopsies. When necessary, explorative thoracotomy was performed. The patients were classified into two main groups according to extension of the tumour (TNM stage I and II versus III and IV).

Each patient provided two consecutive timed overnight urine samples at the time of diagnosis and before treatment. In 29 surgically resected patients with non-small cell lung carcinoma (NSCLC), two overnight urine samples were obtained 3 months after the thoracotomy. 19 (66%) patients were considered to be radically resected. A radical resection was defined as a resection of the primary tumour along with all positive hilar and mediastinal lymph nodes and with histologically confirmed negative margins. No patient died of complications associated with the surgical procedure (operative death). Urine samples following radiation therapy or chemotherapy were not collected due to the possible influence of treatment on urinary albumin excretion.

Urine was collected in standard plastic receptacles without additive. The albumin excretion rate was measured either in fresh urine samples or after storage for less than one week at 4°C. Urinary albumin was assayed by immunoturbidimetry using sheep anti-human albumin and a BM/Hitachi 704 analyser (Boehringer Mannheim, Germany) [14]. The lower detection limit for albumin excretion rate was 0.5 μg/min and the interassay and intra-assay coefficients of variation were 6 and 4%, respectively. The albumin excretion rate was calculated as an average of the two urine samples collected in each patient. Microalbuminuria was defined as a urinary albumin excretion rate of more than 20 μg/min in either or both of the two overnight urine samples according to conventional standards [15].

Table 1. *Characteristics of patients with malignant lung disease according to TNM stage and histopathology*

	n (%)
Initial TNM stage	
I	16 (15.7)
II	20 (19.6)
IIIa	26 (25.5)
IIIb	20 (19.6)
IV	20 (19.6)
Histopathology	
Squamous cell carcinoma	40 (39.2)
Adenocarcinoma	26 (25.5)
Large cell carcinoma	14 (13.7)
Small cell carcinoma	22 (21.6)

Statistics

Urinary albumin excretion rates are expressed as median and range, since they were not normally distributed. Unpaired data were analysed using the Mann–Whitney U test. The X^2 test and Fisher's Exact test were used for comparison of proportions. Univariate survival analyses were calculated using the life-table method of Kaplan–Meier. Survival time was calculated from the date of the confirmed diagnosis to death or to the day of follow-up. Differences between survival curves were tested by the log-rank test. Cox's proportional hazards regression model was used in a multivariate model to estimate the relative importance of multiple factors on survival. A P value of < 0.05 was considered to be statistically significant.

RESULTS

The study population consisted of 102 (61%) patients with primary lung cancer and 65 (39%) with benign diagnoses. Characteristics according to TNM stage and histopathological type in patients with malignant lung diseases are presented in Table 1. Distribution of age did not differ significantly between patients with malignancy and control subjects with benign disorders (median age 58 versus 54 years). The male:female ratio in patients with malignancies and controls was 2.8 and 1.4, respectively.

The prevalence of microalbuminuria (albumin excretion rate > 20 μg/min in either or both urine samples) differed significantly between patients with malignancies and controls (33/102 (32.4%) versus 9/65 (13.8%), $P < 0.01$). The distribution of urinary albumin excretion in the two groups is shown in Figure 1. Patients with malignancies had a significantly higher median value of urinary albumin excretion than patients with benign disorders (13.4 (range 3.9–494.3) versus 8.9 (range 2.4–193.6) μg/min $P < 0.003$, 95% confidence interval of median difference 2.1–7.4 μg/min). No significant age difference was apparent when cancer patients with microalbuminuria were compared with patients without microalbuminuria (median age 60 versus 58 years). Urinary

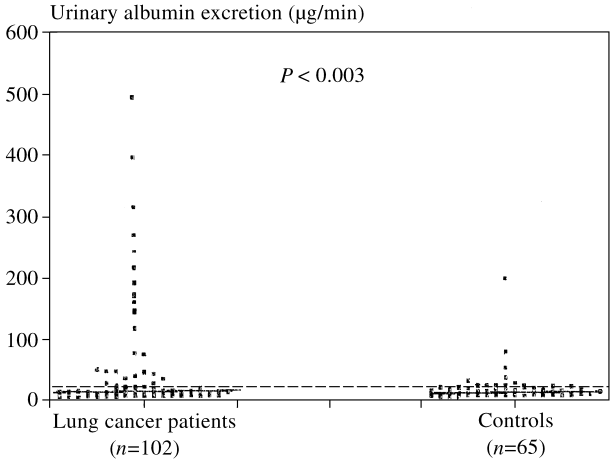

Figure 1. Distribution of urinary albumin excretion in patients with lung cancer and controls. The horizontal lines indicate median values (solid) and upper limit of normal urinary albumin excretion (red—shown as broken line).

Table 2. Urinary albumin excretion rate in patients with primary lung cancer (n=102) *according to TNM stage and histological type*

	Urinary albumin excretion (μg/min)
	Median value (95% CI)
TNM stage	
I and II	8.8 (5–14)
III and IV	13.8 (11–18)
Histopathology	
Squamous cell carcinoma	11.5 (6–15)
Adenocarcinoma	11.7 (7–15)
Large cell carcinoma	14.5 (11–19)
Small cell carcinoma	15.6 (10–21)

95% CI: 95% confidence interval.

albumin excretion rates in patients according to TNM stage and histological type of the tumour are shown in Table 2. Albumin excretion was significantly higher in patients with a large tumour burden (TNM stage III and IV) than in patients with less advanced disease (TNM stage I and II) ($P < 0.003$). There was no significant difference in urinary albumin excretion among the histological types.

The frequency of pre-operative microalbuminuria in 29 surgically resected NSCLC patients was higher compared with the frequency of postoperative microalbuminuria, but the difference did not reach statistical significance (Table 3). Neither pre-operative nor postoperative microalbuminuria had a significant influence on disease-free survival after thoracotomy (data not shown). The frequency of systemic relapse and local recurrence did not differ significantly between resected patients with normal and elevated urinary albumin excretion.

The median duration of follow-up was 28 months (range 23–36). In the univariate survival analysis of the patients with malignant disease, the overall survival rate was 47% after 1 year and 12% after 3 years. Survival curves of patients with and without microalbuminuria are shown in Figure 2. Patients with elevated urinary albumin excretion had a significantly lower survival rate than patients with normoalbuminuria ($P < 0.00001$). The probability of survival 1 and 3 years after diagnosis was 66% and 16% versus 22% and 4%, respectively. If 15 μg/min was selected as a cut-off value for microalbuminuria (a value below the standard range in diabetics and higher than the normal range in the general population), the difference between the two survival curves continued to be significant ($P = 0.03$). In the multivariate model, age, sex, performance status [16], histological type and TNM stage were included (Table 4). When adjusted for these factors, elevated urinary albumin excretion continued to be a significant predictor of survival ($P < 0.001$). Among the other factors, TNM stage and performance status proved the most important. Age, sex and histopathology did not have statistical significance.

Table 3. Prevalence of microalbuminuria in surgically resected patients (n=29) *with non-small cell lung carcinoma before and after operation*

	Microalbuminuria present in	
	One or both samples	Neither sample
Pre-operative samples	10 (34.5%)	19 (65.5%)
Postoperative samples	3 (10.3%)	26 (89.7%)

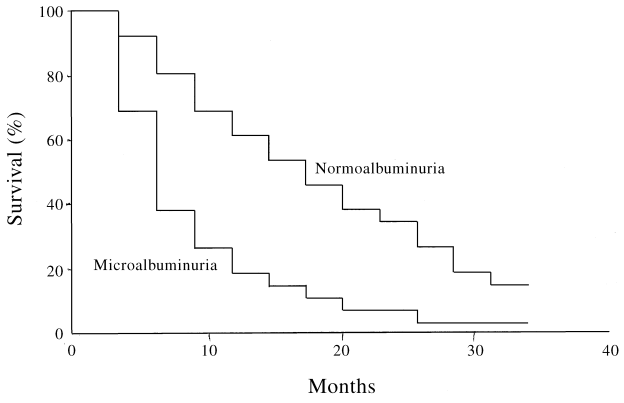

Figure 2. Survival curves of lung cancer patients with normal ($n = 69$) and elevated ($n = 33$) urinary albumin excretion.

DISCUSSION

Renal lesions are frequently described in neoplastic diseases [10, 17]. Histological evidence of glomerular lesions in renal biopsies has been demonstrated in several studies [10, 18, 19]. Electron microscopic and immunohistochemical analyses have demonstrated deposition of tumour-derived antigens and immune complexes on the glomerular basement membranes [20–25]. Circulating immune complexes are frequently identified in patients with malignant diseases [26]. It has also been suggested that lymphokines produced by tumour cells may cause glomerular injury [27]. However, evidence of a causal association between malignancy, immunologically mediated mechanisms and glomerular injury is lacking. Remission of proteinuria after treatment of the malignant disease and relapse of renal manifestations with recurrence of the malignancy may indicate a link between tumour and glomerular injury [10, 28, 29]. We were not able to perform renal histological or immunohistochemical studies in our study.

Table 4. Multivariate survival analysis in patients with malignant pulmonary diseases (n=102)

Variable	Relative risk estimates	95% CI	*P* value
Urinary albumin excretion			
Normoalbuminuria	1		
Microalbuminuria	5.28	1.96–14.89	0.001
Histopathology			
Squamous cell carcinoma	1		
Adenocarcinoma	1.38	0.60–2.18	NS
Large cell carcinoma	1.76	0.71–3.36	NS
Small cell carcinoma	1.65	0.69–2.98	NS
TNM stage			
I and II	1		
III and IV	5.12	1.77–15.48	0.001
Performance status			
0–1	1		
2–4	6.12	1.90–16.51	0.001
Age			
< 50 years	1		
≥ 50 years	1.86	0.63–4.39	NS
Sex			
Male	1		
Female	1.51	0.85–2.84	NS

95% CI, 95% confidence interval; NS, non-significant.

Proteinuria may reflect a paraneoplastic manifestation in some cases of neoplastic disease [18]. Nephrotic syndrome is frequently described in lymphoproliferative disorders [27, 30], but has also been reported in solid tumours [31]. However, subclinical disease is believed to be much more common [32]. This preliminary study indicates a high prevalence (32.4%) of microalbuminuria in lung cancer patients without other conditions known to increase albumin excretion. This is a higher proportion than reported in the general population. The prevalence of microalbuminuria in the general population has been estimated to be 2.2% but is increased in elderly people [33, 34]. The 95th percentile of normal for an overnight albumin excretion rate has been estimated to be 7.6 μg/min [35]. The definition of the lower limit of microalbuminuria is based on studies of diabetic populations. Whether this lower limit can be applied to non-diabetic subjects is unclarified.

Earlier studies have demonstrated an increased prevalence of proteinuria in malignancies [5–7]. The presence of proteinuria is associated with advanced disease and a large tumour burden [6]. Surgical or medical treatment of the malignant disease may reduce the excretion of protein [6]. We used an immunoturbidimetric assay for the determination of low concentrations of albumin in urine. This assay makes it possible to measure albumin in urine below levels detectable by standard laboratory methods used in previously published studies of proteinuria in malignancies. Subclinical renal damage related to the malignant disease may be reflected by low concentrations of urinary albumin found with a high prevalence in our study. Furthermore, albuminuria may reflect isolated glomerular changes or a more widespread dysfunction of vascular permeability. A causal relation between neoplasia and glomerular injury has not been established. Our results provide information indicating a causal association. Urinary albumin excretion was normal in most patients with a small tumour burden. Patients with advanced disease stage had the highest excretion rates. Furthermore, surgical removal of the tumour was followed by a reduced excretion rate of albumin.

A few studies have indicated a relationship between proteinuria and survival in cancer patients [5, 6]. In the present study, using a more sensitive assay for urinary albumin, it has been confirmed that increased urinary albumin excretion is a strong predictor of survival in patients with lung cancer. It has also been demonstrated that microalbuminuria continues to have a significant prognostic impact when adjusted for other known prognostic factors such as TNM stage and performance status.

Further studies are recommended to prove a similar prognostic significance of microalbuminuria in other malignancies. Further studies are also needed to identify a renal morphological correlation to increased urinary albumin excretion and to elucidate whether increased glomerular leakage of albumin is caused by structural or biochemical alterations. It also remains to be clarified whether leakage of albumin is associated with generalised vascular damage or is an isolated renal manifestation.

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