BRITISH JOURNAL OF BIOMEDICAL SCIENCE, 2018
VOL. 75, NO. 1, 50–52
https://doi.org/10.1080/09674845.2017.1372159

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BIOMEDICAL SCIENCE IN BRIEF

Serum sMICA as biomarker in detection of non-small-cell lung carcinoma

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ARTICLE HISTORY Received 2 August 2017; Accepted 3 August 2017

KEYWORDS Lung cancer; serum biomarkers; sMICA

Lung cancer brings a high rate mortality worldwide, almost 85% of cases being non-small-cell lung cancer (NSCLC). The high rate is partly due to the aggressive nature of the neoplasia and that since more than 60% of patients are diagnosed at advanced stages due to the lack of perceivable symptoms at the early stage of tumorigenesis [1]. Staging is crucial: five-year survival rate for patients with advanced disease is <10%, whereas five-year survival rate in patients with stage I disease is >70%. Currently, pathological diagnosis based on biopsies remains the standard methods for early stage NSCLC detection, which has an advantage over the other methods since it can dynamically monitor the aberrant conditions of lung. However, the invasive nature of this technique poses a small but potential clinical risk [2]. Chest X-ray and computed tomography (CT) are also used to detect early stage NSCLC, but it does not improve lung cancer-specific mortality, whilst exposure to the radiation may be harmful [3]. Therefore, robust non-invasive screening methods to detect lung cancer at curable early stage are urgently required.

Several protein biomarkers have been found as non-invasive and cost-effective diagnostic tools for early stage NSCLC, such as CA-125, CA19-9 and CEA. However, the limited sensitivity and specificity call for a need to develop novel biomarkers with high accuracy for the screening of early stage NSCLC. Major histocompatibility complex class I chain-related peptide A (MICA) is frequently expressed on the surface of intestinal epithelium and by many epithelial tumours. MICA is an immune response-induced antigen which was identified as an activator of natural killer cells [4]. Expression of MICA is upregulated by a range of primary tumours including lung, kidney, prostate, breast and colon [5]. Recent studies suggest that in addition to expressing membrane bound MICA, carcinoma cells also have a mechanism to shed MICA into the extracellular domain, generating a soluble form (sMICA). This process leads to a decrease of membrane-bound MICA and an increase of sMICA.

Previous studies have demonstrated that elevation of sMICA is associated with poor prognosis in patients with oral squamous cell carcinoma [6]. Poorly differentiated and late stage osteosarcomas demonstrate higher sMICA levels, making sMICA an excellent prognostic and diagnostic indicator of advanced stages in osteosarcomas [7]. However, the feasibility of sMICA as a biomarker in NSCLC remains largely unknown. We tested the hypothesis of raised sMICA in NSCLC patients that are linked to clinical features of the cancer.

Peripheral blood was drawn from patients and controls at the central hospital of Linyi from May 2010 to January 2014. Sera were obtained from 258 participants: 106 patients with NSCLCs who underwent tumour resection, including adenocarcinoma (89 cases) and squamous cell carcinoma (17 cases); 76 healthy donors randomly selected from those deemed to be healthy by medical examination, and 76 benign lung disease patients (4 chronic hypersensitivity pneumonitis, 24 pulmonary infection, 29 chronic obstructive pulmonary disease, 6 asthma, 6 cryptogenetic organizing pneumonia and 7 asbestosis). The benign lung disease patients had no history of cancer and age ≥18 years. The inclusion criteria for the NSCLC patients were pathologically confirmed NSCLC, age ≥18 years, and had not received any anti-tumour therapy before surgery. Demographic and pathological data, including age, gender and smoking history, were collected. Written consent and approval of the Institutional Review Board of the central hospital of Linyi were obtained to collect specimens from patients undergoing lobectomy for lung cancer at the central hospital of Linyi.

Blood was processed for serum extraction within 1 h and then flash-frozen into liquid nitrogen for long-term storage at −80 °C. Clinical data were collected from the medical records and all cases were staged according to the revised AJCC/UICC 7th edition TNM classification schema [8]. sMICA levels were measured in duplicate by ELISA (R&D Systems, Minneapolis, USA). Continuous variables are presented as median/IQR (range), and categorical variables as frequencies (percentages). The differences of sMICA levels between groups were evaluated by the nonparametric Mann–Whitney U-test or

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the Kruskal–Wallis with Dunn's test determine the relationship between serum sMICA and clinicopathological parameters. Survival curves were plotted by Kaplan–Meier, and the differences in survival time were compared by applying the log-rank test. Multivariate analysis used Cox proportional hazards regression to determine independent prognostic factors that were significant in a univariate Kaplan–Meier analysis. Receiver operating characteristic (ROC) curve was used to interpret the ability of sMICA in discriminating patients from controls. The area under the curve (AUC), sensitivity and specificity at the optimal cut-off were computed. Statistical analysis used SPSS 13. $p<0.05$ was considered statistically significant.

We recruited 106 patients with NSCLC, 76 patients with non-malignant disorders and 76 healthy controls. The age (year) was 65.6 (29–87) in patients with NSCLC, 65.3 (30–89) in 76 healthy controls ($p=0.168$) and 64.9 (28–88) in 76 patients with non-malignant disorders ($p=0.154$). The number of males and females was 73 (68.8%) and 33 (31.2%) in patients with NSCLC, 49 (64.5%) and 27 (35.5%) in healthy controls and 53 (69.7%) and 23 (30.3%) in patients with non-malignant disorders, ($p=0.564$) and ($p=0.484$) respectively.

sMICA levels in healthy controls was 34.3 (8.7–93.6), 37.5 (10.4–118.6) pg/ml in patients with non-malignant disorders and 358.6 (29.4–3675.6) pg/ml in NSCLC patients ($p<0.001$ to both other groups). The clinicopathologic characteristics of the patients are summarized in Table 1. Patients with lymph node metastasis had a significantly higher serum level of sMICA compared with those patients without lymph node metastasis. High sMICA was linked with TNM Stage and advanced tumour stage, whereas no substantial difference was observed between patients' sex, age, tumour size, histology, differentiation, smoking history and serum sMICA levels. We used the median sMICA of 359 pg/ml as the cut-off value in NSCLC patients. Increased sMICA (>359 pg/ml) was found in 63% (67/106) of patients with NSCLC. The prognosis of those patients with high sMICA (>359 pg/ml) was significantly poorer than that of patients with lower sMICA (<359 pg/ml; $p=0.028$).

Univariate analysis showed that tumour stage [hazard ratio HR/95%CI: 3.87 (1.89–9.73), $p=0.013$], lymph node status [HR/95%CI: 2.18 (1.24–7.13), $p=0.04$], TNM stage [HR/95%CI: 3.67 (1.85–8.92), $p=0.014$] and sMICA [HR/95%CI: 1.12 (0.87–6.47), $p=0.001$], each predicted a significantly worse prognosis in NSCLC patients. Clinical prognosis was, however, not associated with sex, age, tumour size, histology, differentiation and smoking history. A Cox proportional hazards model was applied to estimate the effect of sMICA on survival. The crude hazard ratio (HR) of high/low sMICA was HR/95%CI: 1.08 (0.74–4.83), $p=0.002$]. With multivariable analysis, sMICA [HR/95%CI: 1.38 (0.96–5.04), $p=0.014$] and lymph node metastasis [HR/95%CI: 1.26 (0.87–5.46), $p=0.002$] were significantly associated with survival.

Table 1. Relationship between sMICA and clinicopathological factors in patients with NSCLC.

	sMICA (pg/ml)	*P*
Clinicopathological factors		
Gender		0.457
Male (*n*=73)	362.5 (31.5–3445.6)	
Female (*n*=33)	354.6 (30.3–3605.4)	
Smoking history, *n* (%)		0.127
Never smoker (*n*=34)	341.7 (27.9–3746.3)	
Former smoker (*n*=24)	367.5 (34.5–3680.4)	
Current smoker (*n*=48)	351.8 (28.7–3565.4)	
Stage		0.007
I (*n*=58)	217.4 (160.3–3028.4)	
II (*n*=36)	513.4 (207.2–4126.8)	
III (*n*=12)	784.6 (289.4–5576.3)	
TNM stage		0.006
I + II (*n*=83	267.5 (156.4–3743.4)	
III (*n*=23)	613.2 (178.5–5048.6)	
Histology		0.263
Adenocarcinoma (AC) (*n*=89)	356.3 (40.5–3478.6)	
Squamous carcinoma (SCC) (*n*=17)	367.5 (32.5–3764.4)	
Lymph node metastasis		0.002
Yes (*n*=77)	578.2 (219.5–4967.2)	
No (*n*=29)	300.8 (24.4–3288.7)	
Tumour size (cm)		0.146
≤2 (*n*=38)	350.4 (27.2–3584.2)	
>2 (*n*=68)	412.6 (44.8–3766.5)	
Differentiation		0.258
Well + moderate	348.4 (42.7–3367.2)	
Poor	406.4 (56.3–3567.3)	

ROC curve analysis assessed the value of sMICA in NSCLC diagnosis. The AUC was 0.87 [95% CI:0.71–0.91, $p=0.026$]. We chose the point with highest sensitivity and specificity, 70.4 pg/ml, as the cut-off value, where sMICA achieved a diagnostic sensitivity of 74.6% and a specificity of 88.3% (Figure 1).

Serological biomarkers are very important in the management of lung cancer. Previous clinical studies in NSCLC exposed the pros and cons of common biomarkers for diagnostic applications [9], while others underlined their value in disease prognosis and therapy monitoring [10]. From a clinical standpoint, CYFRA 21-1, CEA, CA 125 and SCC still represent the most valuable markers in NSCLC and are primarily used for disease monitoring. However, their prognostic value remains in doubt. Recently, focus has shifted on the discovery of novel prognostic and monitoring markers, as a means to improve clinical management of NSCLC.

High sMICA exists in serum of patients with metastatic pancreatic cancer and advanced hepatocellular carcinoma than those without disseminated disease [11,12]. In the present study, we measured sMICA levels to hypothesize whether sMICA could detect NSCLC patients, from healthy controls: sMICA was indeed elevated in NSCLC patients, and were significantly linked with several aggressive clinicopathological features, such as lymph node metastasis, high tumour stage

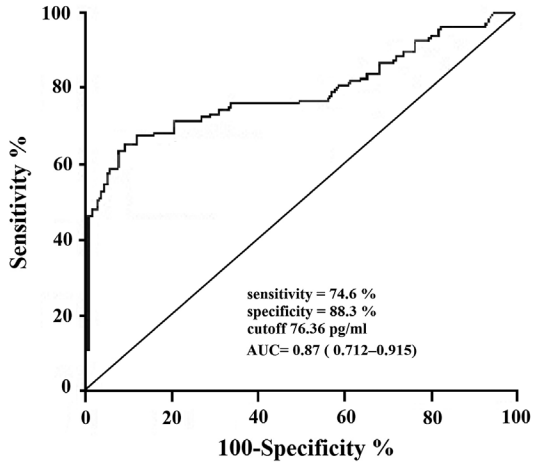

Figure 1. ROC curve of serum sMICA as a tumour marker in NSCLC. Notes: Using a cut off value 76.4 pg/ml, ROC analysis revealed an area under curve (AUC) of 0.79 (p=0.026).

and high TNM stage. These observations suggest that increased sMICA is closely related to the development and progression of NSCLC. Koguchi et al. have reported that elevated sMICA is associated with poor survival in ipilimumab-treated patients [13]. Rebmann et al. have reported that cervical adenocarcinoma patients with high-serum sMICA levels have an increased survival [14]. Multivariate analysis revealed sMICA as an independent predictive factor for survival in patients with cervical adenocarcinoma [15]. Chen et al. have shown that the high expression of MICA indicates poor prognosis for advanced NSCLC patients [5].

Our Kaplan–Meier analysis revealed significantly better survival for patients with low levels of sMICA compared with patients with high levels. Multivariate analysis revealed that high sMICA was an independent predictor for survival. Our results are in agreement with other studies, in which the high sMICA levels has been associated with a poor prognosis [14,15].

This work represents an advance in biomedical science because it shows that sMICA could discriminate NSCLC patients from non-NSCLC controls, so may represent a novel prognostic and diagnostic markers for NSCLC.

Disclosure statement

No potential conflict of interest was reported by the authors.

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