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ORIGINAL ARTICLE

Pleural fluid glucose: A predictor of unsuccessful pleurodesis in a preselected cohort of patients with malignant pleural effusion

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Summary

Purpose: *To assess whether exclusion of patients with conditions that could lead to large fluctuations of serum glucose, would increase the accuracy of pleural fluid glucose in predicting pleurodesis outcome in patients with malignant pleural effusion subjected to bleomycin pleurodesis.*

Methods: *A retrospective analysis of 162 patients with recurrent, symptomatic malignant pleural disease was performed. Patients with diabetes mellitus or other causes of hyperglycemia were excluded, as pleural fluid glucose has been reported to be sensitive to serum glucose fluctuations. Assessment of pleurodesis outcome was based on radiologic appearance 30 days post-bleomycin pleurodesis.*

Results: *Successful pleurodesis was achieved in 64.8% of patients. Univariate analysis showed that pleural fluid glucose (p<0.001), pH (p<0.001), total proteins (p<0.001), albumin (p<0.001) and cholesterol (p<0.05) were significantly lower in patients with pleurodesis failure, while LDH was significantly higher (p<0.05). Pleural fluid glucose was the only independent predictor of pleurodesis outcome and with a cut-off point of 65 mg/dl had a high sensitivity (90.7%) with an acceptable specificity (76.8%) (p<0.001). The regression model exhibiting the highest predictive accuracy included pleural fluid glucose and albumin (sensitivity 89.3%, specificity 84.5%, p<0.001). Furthermore, a product of glucose and albumin less than 152 could predict pleurodesis failure with 88.9% sensitivity and 82.8% specificity (p<0.001).*

Conclusions: *Pleural glucose levels may reliably predict pleurodesis failure in patients without conditions that could lead to hyperglycemia, and its accuracy can increase if combined with pleural fluid albumin in an-easy-to calculate formula.*

Key words: *biomarkers, bleomycin, malignant pleural effusion, pleural fluid glucose, pleurodesis*

Introduction

In patients with cancer, malignant pleural effusions (MPE) represent one of the commonest problems clinicians have to face in their everyday practice. It is estimated that approximately 200,000 patients are diagnosed with MPE annually in the United States [1]. Patients may remain asymptomatic but most often they appear with dyspnea at rest, decreased exercise tolerance, and decreased overall quality of life [2]. Although symptoms can be relieved by a therapeutic thoracentesis, effusion can rapidly recur.

Chest tube thoracostomy with subsequent pleurodesis is the most commonly used modality for managing MPE worldwide [3]. Unfortunately, pleurodesis attempts fail in 10 to 40% of patients with recurrence of pleural fluid and dyspnea [4]. As pleurodesis is associated with considerable cost and morbidity, the identification of patients who would experience a pleurodesis failure would be desirable [4].

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The utility of various biochemical parameters of MPE in predicting pleurodesis outcome is still controversial. Several studies have been published in the literature dealing with the relation between pleural fluid pH, glucose, CRP, cholesterol, adenosine deaminase (ADA) or elastance and pleurodesis outcome [5-9]. Among them, low glucose concentrations and pH values in the pleural fluid have been traditionally associated with increased tumor burden and decreased success of pleurodesis [5]. However, on the one hand, discordant pH cut-off values have been reported, while, on the other, the prognostic accuracy of glucose levels has been questioned due to its sensitivity to serum glucose fluctuations [2,3].

The aim of the present study was to assess whether exclusion of patients with conditions that could lead to large fluctuations of serum glucose, such as diabetes or treatment with medications that could lead to hyperglycemia, would increase the accuracy of pleural fluid glucose in predicting pleurodesis outcome in patients with MPE subjected to bleomycin pleurodesis.

Methods

Inclusion/exclusion criteria

After approval by the institutional review board of "Sotiria" General Hospital, the files of the patients with MPE referred to our department between September 2005 and May 2013 were retrospectively investigated. The inclusion criteria were: first pleurodesis attempt in patients with biopsy-proven malignancy and recurrence of MPE after therapeutic thoracentesis; improvement of patients' symptoms and complete lung expansion on chest radiography after therapeutic thoracentesis; acceptable general medical condition rendering pleurodesis possible, as assessed by a Karnofsky performance score of 70-100; and survival of more than one month after pleurodesis. Exclusion criteria included patients with small cell lung cancer, loculated effusions, diabetes mellitus and treatment with drugs that could lead to hyperglycemia, such as corticosteroids, beta blockers, thiazide diuretics, niacin and some antipsychotic agents like quetiapine, aripiprazole, olanzapine, risperidone, clozapine, ziprasidone which have been associated with a direct increase of glucose blood levels. Among 286 patients with MPE, 162 fulfilled our criteria.

Technical aspects

All bleomycin pleurodesis attempts in our department were performed at the bedside in a standardized protocol by a trained respiratory physician [10]. In all cases, a small bore tube (10-14 Fr) connected to a closed gravity drainage bag system was placed in the seventh or eighth intercostal space at the posterior axillary line and was left in site until the pleural space was adequately drained as evidenced by <150 ml/24 hrs of fluid drainage and radiographical evidence of lung re-expansion. When all the above criteria were met and at 15 min after instillation of 3 mg/kg (maximum 250 mg) of lidocaine 1%, 60 IU of bleomycin in 100 ml of sterile saline were instilled via the chest tube and the tube was clamped for two hours. The chest tube was removed when the pleural fluid drainage remained <150 ml/24 hrs and the chest X-ray showed complete lung expansion. No patient received systemic corticosteroids or any non-steroid anti-inflammatory drugs one week before and 30 days after pleurodesis.

Data assessed

The demographical and clinical data, as well as the biochemical parameters obtained from the first diagnostic thoracocentesis in the pleural fluid were recorded from the patients' files. The data included age, gender, primary malignancy Karnofsky performance score and the pleural fluid biochemical parameters, i.e. glucose, albumin, total proteins, pH, LDH and ADA levels. Cholesterol levels, triglycerides and amylase in the pleural fluid were also recorded if available.

Response assessment

Each patient had a pre-drainage baseline posteroanterior (PA) radiograph. Post-pleurodesis PA radiographs were obtained before removal of the chest tube and within one week and 30 days after removal. Assessment of response was based on radiologic appearance. The radiographic response 30 days after removal of the chest tube was compared with the post pleurodesis PA radiography before removal of the chest tube and was classified as: i) complete response, when there was no re-accumulation of pleural fluid, ii) partial response, when re-accumulation was above the post-pleurodesis but below the pre-pleurodesis level, and iii) no response, if re-accumulation was above the pre-pleurodesis level. Complete and partial responses were considered as successful pleurodesis [11]. All radiographs were examined by two radiologists blinded to the pleural fluid test results to ascertain the reproducibility of the decision. If the decisions of the two investigators were not consistent, a third investigator gave the final decision.

Statistics

Continuous variables are described as mean±standard deviation and median (Interquartile range, IQR) for symmetric and asymmetric distributions, respectively. Categorical data are presented as frequencies (%). The Kolmogorov–Smirnov test and graphical methods were used in order to assess whether the continuous variables followed a Gaussian pattern. Comparisons

Table 1. Characteristics of the population studied

	Pleurodesis		
	Successful (N=105)	*Failed (N=57)*	*p value*
Age, years ± SD	70.0 ± 6.8	69.6 ± 7.3	NS
Range	52-82	53-80	
Gender N (%)			
Female	35 (33.3)	16 (28.1)	NS
Karnofsky score ± SD	82.9 ± 7.3	84.2 ± 6.2	NS
Primary site of tumor (N)			
Lung	99	51	NS
Breast	4	2	NS
Stomach	2	3	NS
Unknown	0	1	NS

SD:standard deviation, NS:Not significant

of continuous variables between independent groups were performed utilizing Student's unpaired t-test and Mann-Whitney non parametric test, as appropriate. Linear relationships between parameters were assessed by calculating Pearson's correlation coefficient or the non-parametric Spearman's rho, as appropriate. Receiver Operating Characteristic curves (ROCs) were used in order to determine the prognostic accuracy, sensitivity, specificity and area under the curve (AUC) of the parameters, as well as to obtain the appropriate cut-off points. Binary logistic regression was utilized in order to determine predictors. Forward stepwise selection was utilized to extract the final model. All tests were two-sided. Differences were considered as statistically significant if the null hypothesis could be rejected with >95% confidence ($p<0.05$).

Results

The study population consisted of 162 patients (111 men and 51 women), with a mean age of 70±7 years (range 52-82) who underwent pleurodesis for recurrent symptomatic MPE. All patients had metastatic pleural carcinomas. No one had malignant mesothelioma. The characteristics of the population studied are shown in Table 1. Bleomycin pleurodesis was successful (complete and partial responses) in 105 (64.8%) of patients.

Univariate analysis showed that pleural fluid glucose ($p<0.001$), albumin ($p<0.001$), total proteins ($p<0.001$), pH ($p<0.001$) and cholesterol ($p<0.05$) were significantly lower in patients with pleurodesis failure compared to patients with successful pleurodesis, while LDH was significantly higher ($p<0.05$). Laboratory data are summarized in Table 2. Pleural fluid glucose and pH demonstrated a strong correlation ($r=0.71$, $p<0.001$) and the same was observed for pleural fluid, total proteins and albumin ($r=0.85$, $p<0.001$).

ROC curves were calculated to assess the accuracy of the measured parameters in predicting pleurodesis outcome and to identify optimal cut-off values (Figure 1). The optimal cut-off points together with AUC, sensitivity, specificity, positive and negative predictive values for all parameters studied are shown in Table 3.

Binary logistic regression was used to determine the predictors of pleurodesis failure, as well as to identify multivariate models with increased predictive accuracy. All parameters having statistically significant AUC in the ROC analysis were assessed. Pleural fluid glucose with a cut-off point of 65 mg/dl had a high sensitivity and specificity (90.7 and 76.8%, respectively, $p<0.001$) and was identified as the only independent predictor of pleurodesis failure. The regression model incorporating pleural fluid glucose and albumin concentration presented the highest predictive accuracy (sensitivity 89.3%, specificity 84.5%, Nagelkerke R^2: 0.63, AUC: 0.919, $p<0.001$) (Figure 2).

Taking into account the parameters included in the most accurate logistic regression model, we examined whether we could design an easy-to-calculate formula presenting comparable predictive accuracy. A product of glucose and albumin less than 152 could predict pleurodesis failure with 88.9% sensitivity and 82.8% specificity ($p<0.001$; Table 3).

Discussion

In our study, pleural fluid glucose was the only independent predictor of pleurodesis failure. This finding is of special importance considering that patients with diabetes mellitus or those re-

Table 2. Comparison of pleural fluid biochemical parameters (before pleurodesis)

Biochemical parameters	*N*	*Successful pleurodesis*	*Failed pleurodesis*	*p value*
		Median (IQR)	*Median (IQR)*	
Glucose (mg/dl)	161	101 (67-138)	40.5 (22-61)	< 0.001
Albumin (g/dl)	160	2.6 (2.4-2.9)	2.0 (1.8-2.4)	< 0.001
Total proteins (g/dl)	161	4.5 (4.1-4.9)	3.6 (3.2-4.4)	< 0.001
pH	162	7.36 (7.32-7.39)	7.24 (7.20-7.33)	< 0.001
LDH (IU/L)	161	280 (202-472)	370.5 (253-738)	<0.05
ADA (U/L)	137	7 (5-14)	6 (5-8.5)	NS
Cholesterol (mg/dl)	51	87 (67-102)	63 (46-80)	<0.05
Triglycerides (mg/dl)	49	30 (20-46)	27 (20-34)	NS
Amylase (mg/dl)	38	47 (31-64)	37 (22-48)	NS

IQR: interquartile range, LDH: lactate dehydrogenase, ADA: adenosine deaminase, NS: not significant

Table 3. Relative predictive accuracies of biochemical parameters for identifying pleurodesis failure

Predictor	*Optimal threshold*	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*p value*
Glucose (mg/dl)	<65	0.896	90.7	76.8	68	94	<0.001
Albumin (g/dl)	<2.3	0.799	74.5	82.5	70	86	<0.001
Total proteins (g/dl)	<4.2	0.731	74.5	64	53	82	<0.001
pH	<7.32	0.771	72.7	73.8	60	83	<0.001
LDH (IU/L)	>300	0.618	63.6	53.4	43	73	<0.01
Glucose x Albumin	<152	0.92	88.9	82.8	74	93	<0.001

AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value, LDH: lactate dehydrogenase

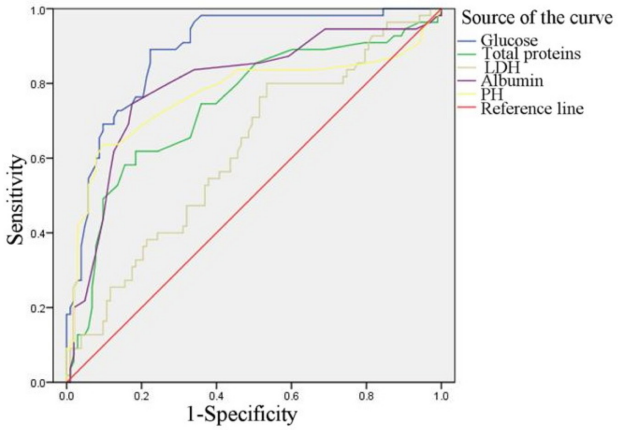

Figure 1. Receiver operating characteristic curves of the pleural fluid biochemical parameters for distinguishing pleurodesis outcome.

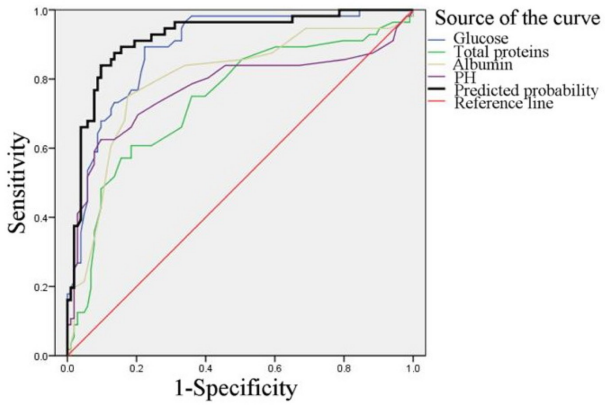

Figure 2. Receiver operating characteristic curve of the regression model for distinguishing pleurodesis outcome.

ceiving drugs that could lead to hyperglycemia were excluded from our study in order to avoid possible bias due to large fluctuations of serum glucose. In this specific cohort of patients, the success rate of bleomycin pleurodesis was 64.8% which is consistent with the current literature [12-16].

Although there are studies showing that pleural fluid glucose levels below 60 mg/dl are associated with pleurodesis failure [12], its sensitivity to predict pleurodesis outcome is not high. However, it should be pointed out that all previously reported studies have included a non-preselected cohort of patients [11] despite the fact that pleural fluid glucose is sensitive to glucose fluctuations in serum and this might have influenced its predictive accuracy. To our knowledge, this is the first study to demonstrate pleural glucose as a predictor of pleurodesis failure in a preselected cohort of patients. A

possible mechanism explaining this finding could be a higher invasion of the pleural membrane by cancer cells. In such a case, low pleural fluid glucose levels would be expected due to increased pleural membrane metabolism by malignant cells and/or consumption of glucose by pleural fluid constituents such as leukocytes and free malignant cells [17]. Furthermore, the higher tumor burden might lead to an abnormal transfer of glucose across the diseased pleural membrane [17]. Consequently, if the malignant disease is advanced to the point where the pleural mesothelial surface is covered by malignant deposits, thus, limiting the interaction between the sclerosing agent and the normal pleural mesothelial surface, the fibrotic response might be attenuated [18].

Another interesting result was that pleural fluid albumin lower than 2.3 g/dl was associated with pleurodesis failure having the highest specificity between all of the parameters examined. A possible explanation of this finding is that activation of the pleural mesothelial monolayer by malignant cells causes a breach in the integrity of the pleura and results in altered shape and gap formation between mesothelial cells causing leakage of proteins and fluids into the pleural space [18]. Moreover, inflammation of the pleura may result in a compromised pleural microvasculature with consequent increased permeability and further fluid and protein leakage into the pleura [18]. As total proteins and albumin of the pleural fluid have been found to correlate with pleural inflammation [1], low pleural fluid albumin levels might reflect a low-grade pre-pleurodesis inflammation of the pleura, and thus, bleomycin infusion may be less effective or completely ineffective.

In our population, pleural fluid pH was significantly lower in patients with pleurodesis failure. However, its sensitivity and specificity for predicting pleurodesis outcome was quite low. Previously, it has been reported that a low pleural fluid pH (<7.2) correlates with the extent of intrapleural tumor burden, thus indicating the outcome of pleurodesis. However, although some authors support the association between pleural fluid pH and pleurodesis outcome [5,12,19,20], other studies have not detected such an association [21-24]. Our results are in accordance with the results of Heffner et al. [21] who reported that pleural fluid pH has only modest predictive value for predicting pleurodesis failure and should be used with caution, if at all, in selecting patients.

LDH is a well-known, useful parameter for monitoring pleural inflammation [25]. However, in our study its sensitivity and specificity for predicting pleurodesis failure was low (63.6% and 53.4%, respectively).

Although it has been demonstrated that pleural fluid ADA level is superior than pleural fluid pH and albumin level in the prediction of pleurodesis success [9,26], this was not demonstrated in our study. It should be pointed out however, that pleural fluid ADA has been suggested to constitute a predictor of pleurodesis outcome mainly in patients with malignant mesothelioma [9], but such patients were not included in our study. In addition, the small size of these studies makes the extraction of sound conclusions difficult.

Cholesterol levels were significantly lower in patients with pleurodesis failure, while triglycerides and amylase were not different between the two study groups. Nevertheless, these markers were available in about one third of the patients studied and thus safe conclusions could not be extracted.

As a next step, we examined the utility of combining tests using multivariate logistic regression analysis and incorporating all the parameters exhibiting significant AUC in the ROC analysis. Interestingly, we found that the model including glucose and albumin pleural fluid concentration achieved the highest sensitivity and specificity; a product of glucose and albumin less than 152 could predict pleurodesis failure with 88.9% sensitivity and 82.8% specificity. To our knowledge, we propose for the first time an easy-to-calculate parameter which allows for the pre-determination of pleurodesis success. However, this finding should be further evaluated in larger studies.

The present study has some limitations. The main limitation is its retrospective design. However, we studied a large population and this allows us to draw some preliminary conclusions that should be confirmed in well-designed prospective studies. Furthermore, patients with MPE who are subjected to pleurodesis may have a Karnofsky performance score lower than 70. In our study we included patients with Karnofsky performance score over 70 as it has been reported to have an association with better pleurodesis outcomes [9]. However, we have no reason to believe that this may have altered the predictive accuracy of pleural biomarkers. Finally, the respiratory physician who performed pleurodesis procedures was not always the same. However, pleurodesis was performed in a standardized protocol by trained respiratory physicians according to recent guidelines [22].

In conclusion, our findings suggest that pleural glucose levels may reliably predict pleurodesis fail-

ure in patients without conditions that could lead to hyperglycemia. Furthermore, we propose for the first time an easy-to-calculate formula which allows for a highly accurate pre-determination of pleurodesis success. These findings should be evaluated in larger well-designed prospective trials.

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