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ORIGINAL ARTICLE

Is the needle still needed? Relationship between laboratory features of pleural effusion and results of lung CT examinations in patients with pneumonia and lung cancer

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Abstract

Introduction and Objective. Thoracocentesis is an invasive procedure routinely performed in the diagnosis of causes for the presence of pathological fluid in the pleural cavity. In many patients, a computed tomography scanning (CT) is also performed to diagnose the cause of the presence of fluid in the pleural cavity. The diagnostic value of CT is particularly high in situations in which performing thoracocenthesis could be associated with an increased risk of complications. The aim other study was to assess the relationship between the objective radiological features and the results of laboratory tests of fluid collected by thoracocenthesis in patients with pneumo-nias (n=18) and lung cancer (n=35).

Materials and method. The examined group consisted of the patients with pneumonia (n=18) and lung cancer (n=35) which resulted in the presence of fluid in the pleural cavity. In the patients thoracocentesis, CT lung scanning was also performed, according to the medical indications. Three scans with the greatest amount of fluid were identified, and the mean density of the fluid expressed in Hounsfield units was calculated within the area. These calculations were compared with the results of laboratory fluid tests.

Results. The maximum number of Hounsfield units (HU) was significantly lower in the group of lung cancer patients, compared to those diagnosed with pneumonia (74.3% sensi-tivity and 55.6% specificity). The pH of pleural fluid was significantly lower in patients with lung cancer, compared to those with pneumonia (74.3% sensitivity and 66.7% specificity).

Conclusions. According to the results, radiological differentiation of pneumonia and lung cancer resulting in pleural effusion, to some extent is possible; however, the needle is still needed.

Key words

lung cancer, pneumonia, pleural effusion

INTRODUCTION

The pleural cavities are physiologically filled with about 0.26 mL of fluid/kg body weight, which prevents friction between the two pleural layers [1, 2, 3]. Excess of the fluid is always associated with pathological processes. Apart from the clinical symptoms, such as dyspnea and suppressed percussion on physical examination of the chest, as well as the reduction of respiratory sounds in auscultation, the fluid can be visualized by many imaging techniques. Chest X-ray is the simplest examination that allows assessment of the presence of fluid in the pleural cavity. Ultrasonography is a convenient and mobile examination that helps to evaluate the mutual position of the anatomical structures of the chest and abdominal cavity, e.g. the edge of the liver, and to determine the safest location for thoracocentesis. The presence of pleural effusion can result from many reasons of which malignancy or pneumonia occur the most often [4]. In many patients, a computed tomography scanning (CT) is performed to diagnose the cause of the presence of fluid in the pleural cavity. However, most information can be obtained from laboratory tests of fluid collected during thoracocentesis. The differentiation of fluid types into exudate and transudate is most often performed on Light's criteria, based on the comparison of blood and pleural fluid parameters, such as total protein concentration, lactate dehydrogenase (LDH) concentration and its activity. Light's criteria are as much as 98% sensitive in the detection of exudate [5].

Thoracocentesis is an invasive procedure routinely performed in internal medicine as part of the diagnosis of the causes of the presence of pathological fluid in the pleural cavity, and in selected cases also from therapeutic indications in order to remove a significant volume of the fluid causing mechanical compression of the lung, and related clinical symptoms. On the other hand, the advantage of CT over

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thoracocentesis results from its non-invasive nature, which is why, in many cases, it is performed before the patient is qualified for pleural puncture.

OBJECTIVE

The aim of the study was to assess the relationship between the objective radiological features and the results of laboratory tests of fluid collected by thoracocentesis. Finding statistically significant correlations could increase the diagnostic and prognostic value of computed tomography. The diagnostic value of CT could be particularly high in situations where performing thoracocentesis would be associated with an increased risk of complications; in such cases, the radiological parameters could support the decision to perform or withdraw from invasive diagnostics.

MATERIALS AND METHOD

Patients with pleural effusions (exudates) stated in chest CT and who underwent thoracocenthesis within one week were included in the study. The classification of pleural effusion was based on Light's criteria, the exudate was diagnosed when at least one of the following criteria was met:

- pleural fluid total protein/serum total protein ratio >0.5;
- pleural fluid LDH/serum LDH ratio >0.6.

Laboratory tests of the fluid were performed in the Central Hospital Laboratory in PSK4 Lublin, Poland.

The examined group consisted of patients with pneumonias (n=18) and lung cancer (n=35) hospitalized in the Department of Lung Diseases and Tuberculosis in Independent Public Clinical Hospital No. 4 in Lublin, Poland, which confirmed by clinically overt and proved in radiological examinations (chest X-ray, computed tomography of the chest, ultrasound of the pleural cavity) the presence of fluid in the pleural cavity. The diagnosis of pneumonia was made based on the clinical assessment, radiological and laboratory blood and sputum tests. Malignant pleural effusion was determined by the previous results of studies, such as biopsy or cytology. The characteristics of the study group are presented in Table 1.

In patients from the group described above, after determining medical indications, excluding contraindications and obtaining the patient's informed consent, diagnostic, therapeutic or diagnostic-therapeutic thoracocentesis was performed. Before each procedure, the patient's informed consent was obtained, the lack of which was the only absolute contraindication to thoracentesis.

The procedures were carried out in a classic way: a needle (or catheter with a mandrin, depending on the clinical situation) was inserted into the chest wall, in close proximity to the upper edge of the rib limiting a given intercostal space, after prior anaesthesia of the puncture area with lidocaine solution. The optimal puncture site was most often determined as a result of ultrasound examination of the chest immediately before the procedure, less often chest tomography, or on the basis of a chest radiograph and percussion. Then, using a sterile thoracocentesis kit consisting of a drainage system and a container, the liquid was aspirated, usually not exceeding a volume of 1.5 l in one procedure. At the end of the procedure, the needle or drain was removed. Samples for laboratory tests, depending on the needs of the clinician, were sent for laboratory tests, and the remaining material was disposed of in accordance with the hospital's internal recommendations for the management of biological waste.

Table 1. Characteristics of demographic-clinical variables in patients with lung cancer or pneumonia

Variable	Lung cancer (n=35)	Pneumonia (n=18)	p
Gender			
Females	11 (31.4%)	9 (50%)	0.3069
Males	24 (68.6%)	9 (50%)	
Age [years]			
Median	69.0	79.0	0.0758
Range (min-max)	(45–83)	(31–96)	

The CT imaging from apices to bases of the lungs was performed in every patient in the supine position during inspiration and holding the breath during administration of intravenous contrast on a 64-row GE scanner. All images were acquired with a standard dose protocol using the following parameters: 120 kV of tube voltage, tube current of 50–300 mA with automatic exposure control, pitch – 0.9, tube rotation time – 0.6 sec, matrix – 512 × 512 mm, slice thickness – 2.5/1.25 mm.

All of the chest CT scans used in the study were then evaluated by a radiologist with 15 years of experience in chest CT scans, blinded to clinical data. The radiologist assessed the CT of patients before the thoracocentesis performed within seven days of the invasive procedure. Three scans with the greatest amount of fluid were identified, defined as its largest antero-posterior dimension. On each of the three scans, the maximum area (ROI- Region of Interest) was drawn, covering only the fluid and the mean density of the fluid expressed in Hounsfield units (HU), calculated within the area. The average HU value for the three tested scans was calculated and compared with the results of laboratory fluid tests.

The collected data was analyzed using statistical software Statistica (v. 13 PL) and MedCalc (v. 15.8 PL). Categorized data was presented in the form of numbers and percentages. Due to the different than normal distribution of continuous data, the median was used as a measure of aggregation, and the dispersion was presented using the minimum-maximum range. Comparison of categorized data between the studied groups was performed using the chi square test and continuous data comparison between the study groups was performed using the Mann-Whitney U test. The diagnostic usefulness of selected variables was assessed with the use of ROC curves (the area under the curve was estimated – AUC and the 95% confidence interval for this value – 95% CI). The correlation between the selected variables was assessed using the Spearman's rank correlation test.

The protocol of this study was reviewed and approved by the Ethics Committee of the Medical University in Lublin (No. K-0254/161/2021).

RESULTS

The study groups of patients with lung cancer and pneumonia were similar in terms of basic demographic-clinical characteristics (Tab. 1). Detailed data on the comparison of radiological and laboratory variables of pleural fluid with lung cancer or pneumonia are provided in Table 2.

Table 2. Comparison of radiological and laboratory characteristics of pleural fluid accumulating in patients with lung cancer or pneumonia

Variable	Lung cancer (n=35)	Pneumonia (n=18)	p
Maximum number of HU units			
Median	66.0	80.5	0.0321
Range (min-max)	(39.0-159.0)	(50.0-201.0)	
Maximum fluid volume [ml]			
Median	77.0	65.0	0.0250
Range (min-max)	(20.0-137.0)	(23.0-109.0)	
pH			
Median	7.3	7.5	0.0100
Range (min-max)	(6.9-8.0)	(7.0-8.5)	
Atypical cells			
Median	0.0	0.0	0.0191
Range (min-max)	(0.0-64.0)	(0.0-2.0)	

Significantly lower values were noted in the range of the maximum number of Hounsfield units (HU) of pleural fluid in the group of lung cancer patients, compared to those diagnosed with pneumonia (Fig. 1). In turn, the maximum amount of fluid that was visible in CT (anteroposterior dimension) was significantly higher in patients with lung cancer compared to those with pneumonia (Fig. 2). In contrast, the pH of pleural fluid was significantly lower in patients with lung cancer compared to those with pneumonia (Fig. 3). In addition, atypical cells in preparations of sediment obtained from pleural fluid were significantly more common in patients with lung cancer compared to those with pneumonia (Fig. 4). Detailed data on the sensitivity and specificity of radiological and laboratory variables of pleural fluid in patients with lung cancer or pneumonia are provided in Table 3.

The maximum HU number of pleural fluid (cut-off point ≤77 HU) was characterized by 74.3% sensitivity and 55.6% specificity in the differentiation of patients with cancer and pneumonia. In turn, the maximum anteroposterior dimension of the fluid measured in CT (cut-off point >73 mm) was characterized by 60% sensitivity and 72.2% specificity in the differentiation of patients with cancer and pneumonia.

The pH of pleural fluid (cut-off point ≤7.3) was characterized by 74.3% sensitivity and 66.7% specificity in the differentiation of patients with cancer and pneumonia.

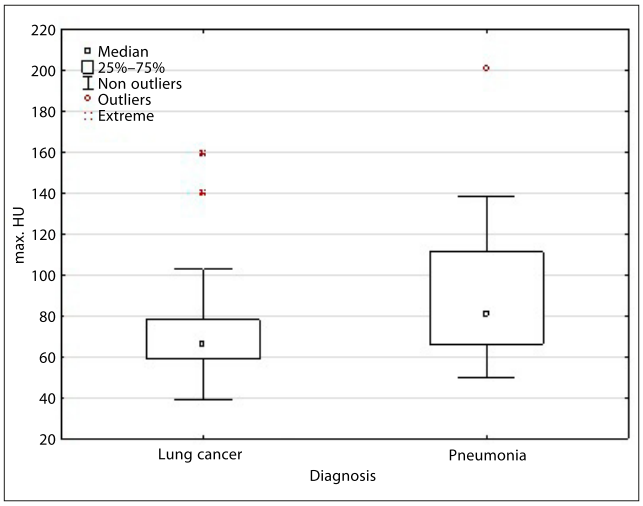

Figure 1. Comparison of maximum HU values depending on the diagnosis of lung disease

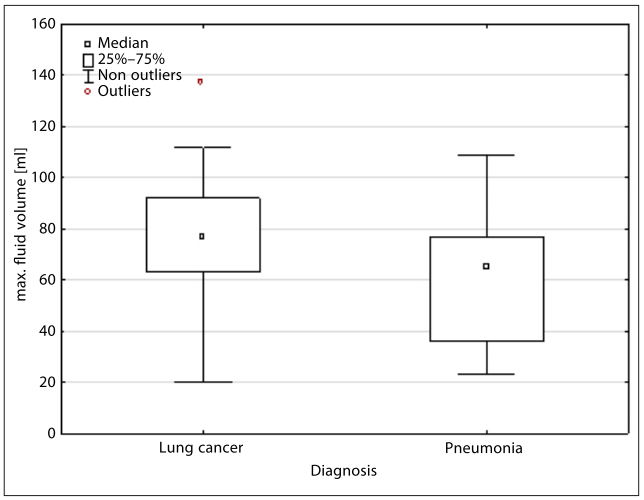

Figure 2. Comparison of the maximum amount of fluid in CT (the largest anteroposterior dimension) depending on the diagnosis of lung disease

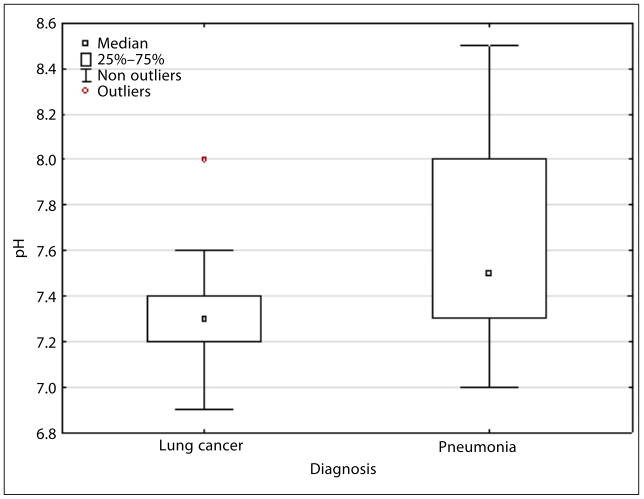

Figure 3. Comparison of the pH value of the fluid depending on the diagnosis of lung disease

The number of atypical cells in the pleural fluid sediment was characterized by 35.7% sensitivity and 100% specificity in the differentiation of patients with cancer and pneumonia.

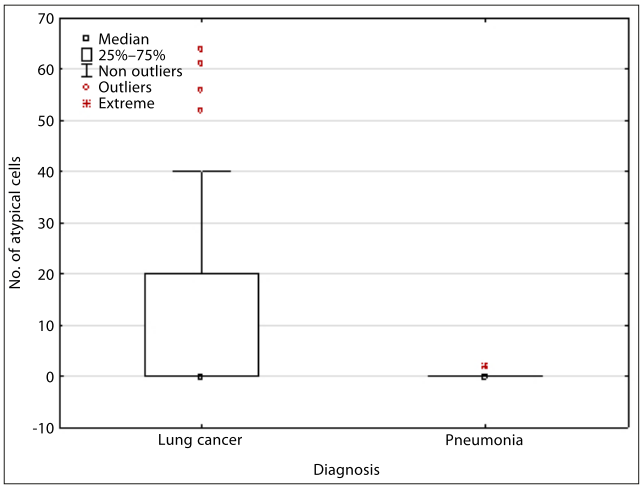

Figure 4. Comparison of the number of atypical cells depending on the diagnosis of lung disease

Table 3. Evaluation of selected variables describing the characteristics of pleural fluid and peripheral blood in terms of their diagnostic usefulness in differentiating lung tissue disease states (cancer vs inflammation)

Variable	Sensitivity (%)	Specificity (%)	Cut-off value	AUC (95%CI) Median [Range (min-max)]	p
Maximum of HU units of pleural fluid.	74.3	55.6	≤77 HU	0.68 [0.54-0.80]	0.0221
Maximal volume of pleural fluid [ml]	60	72.2	>73 mm	0.69 [0.55-0.81]	0.0148
pH (pleural fluid)	74.3	66.7	≤7.3	0.71 [0.56-0.83]	0.0054
Atypical cells in the pleural fluid sediment	35.7	100	>2	0.66 [0.50-0.79]	0.0023

DISCUSSION

Lung cancer and pneumonia can both be the reason for an exudative pleural effusion, containing a substantial amount of proteins, lactate dehydrogenase and cells in comparison with transudate [6]. Common pathomechanism for pleural effusion, both in pneumonia and lung cancer, is the increased permeability of endothelium of blood vessels. This might be accompanied by a change in oncotic and hydrostatic pressure between the vascular bed and the extracellular compartment. The main cause of malignant exudate is the over-production of fluid due to a loss of tightness of blood vessels caused by cytokines produced by cancer cells, and subsequently by leukocytes and pleural cells (mesothelium). The essential meaning attributes to VEGV (Vascular Endothelial Growth Factor), interleukins IL1-beta, IL6, IL8, IL23, TNFalpha (tumour necrosis factor alpha) and CCL2 (C-C motif chemokine 2) from among IL8 and CCL2 are produced mostly by the mesothelium. The level of lymphocytes Th17 is noticeably increased among all subtypes of leukocytes [7].

Another cause of fluid over-production is cachexia, simultaneous with decreased concentration of albumin, which leads to the lowering of oncotic pressure. On the other hand, there is often observed an insufficiency of lymphatic drainage in patients suffering from lung cancer, which is due to possible metastases inside the lymphatic nodes and vessels [7]. In the case of pneumonia, there is also an increased level of pro-inflammatory cytokines. Their production, however, is different because of the lack of malignant cells. Moreover, in this case, lymphatic drainage is supposed to be efficient which could explain the higher amount of pleural fluid in the population of patients with lung cancer, compared to patients with pneumonia.

In the light of the presented study, the specificity of the presence of atypical cells in lung cancer is 100%; however, it seems risky to rely on these results since those atypical cells might be also found in parapneumonic fluid. In both cases, the description 'atypical cells' usually refers to reactive mesothelial cells that undergo hypertrophy, change their shape to cubicle, and migrate into the pleural cavity. In the standard microscope observation of fluid sediment, these cells look similar to malignant epithelial cells (e.g. lung cancer cells), therefore they might be mesothelial or cancer cells (or both) in patients suffering from lung cancer [8]. The full range of pathomorphological tests (cytology) are required to distinguish between the two types of cells.

The substantially lower pH in patients with lung cancer is compelling. Decreased pH might be explained by numerous cells with anaerobic metabolism that may undergo necrosis, and releasing acid content into pleural fluid. In the current study, the patients had advanced lung cancer and, according to Rodríguez-Panadero et al., the pH of fluid corresponded with the extent of pleural infiltration [9]. It is worth noting that in the current study, patients with empyema were excluded, and only patients with parapneumonic fluid (only one patient had some bacteria in the culture of pleural fluid) included. In the case of adding empyema to the group of patients with pneumonia, lower pH levels can be predict since the typical pH in empyema is < 7.2 [10]. According to Good et al., pleural fluid pH < 7.3 is associated with empyema and malignancy, but not uncomplicated parapneumonic fluid [11]. Therefore, it should be emphasized that a decreased pH level could be helpful for distinguishing between malignant and parapneumonic fluid.

Some studies conducted on the usefulness of fluid enhancement assessed in the CT study have shown the importance of radiological evaluation of fluid in differentiating between exudate and transudate [12]. However, the current study only concerns exudates typical for malignancy and pneumonia. Additional signs (fluid loculation, pleural thickness) should also be taken under consideration to provide more information useful in the differentiation between malignant and benign pleural effusion [13].

Higher maximum density (measured with Hounsfield Units) in parapneumonic fluid compared with the malignant one, and no significant difference in median or mean density seems to be curiosity rather than an essential tip for physicians. In daily practice, this measurement is burdened with the risk of making a mistake if the region of interest involves adjacent tissues of a different density (e.g. bones or aerated lung). In the current study, the risk of that type of mistake was avoided thanks to the participation of the experienced radiologist.

Limitations of the study. Despite some interesting observations, the current study also has some limitations. The first of these is the relatively small group of examined patients. In the opinion of the authors, the results obtained can be treated rather as an attempt to search for new, but simple to apply, clinical indicators that would help in the radiological differentiation of the causes of pleural effusion, especially in the cases of lung cancer and pneumonia. As mentioned above, the radiological measurement of density of the pleural fluid would not be convenient in daily routine and could be burdened with the risk of measuring error.

Another limitation is the lack of full homogenity of the group. The patients with lung cancer were not divided into subtypes of cancer and the group of patient with pneumonia did not include cases of pleural empyema. It also cannot be ruled out that some lung cancer patients also had some component of inflammation, which may have affected the results of both the radiological and laboratory tests.

CONCLUSIONS

The issue of the usefulness of computed tomography in differentiating the causes of pleural effusion requires further research. The presence of atypical cells is clearly useful for differentiation; the remaining parameters do not seem relevant. Low pH is indicative of cancer, but it could also be low with complicated inflammatory fluid (infected, empyema). The false diagnosing of lung cancer as simple pneumonia leads to delayed treatment and premature death. Hence, it is legitimate to perform extra diagnostic tests if there are any doubts (e.g. bronchoscopy, cytology, VATS). In the authors' Clinic, any new pleural fluid is routinely sent for additional tests (cytology, culture, tuberculosis). It is worth remembering the so-called 'six-week rule' about radiological follow-up after six weeks of cured pneumonia – the features of pneumonia are expected to fade away in patients younger than 50 years of age (in the elderly, it could take 12 weeks or more) [14]. As the opposite, the signs of malignancy will rather progress or just be more plainly visible. In general, radiological differentiation of the cause of fluid is risky, although, according to the obtained results, to some extent it is possible.

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