

**Cytomorphology of Adenocarcinoma Metastasis in Pleural Effusion Fluid
at the H. Adam Malik Central General Hospital Medan in 2015-2017**

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ABSTRACT

Background: Lung cancer most often causes malignant pleural effusion and the most common type is adenocarcinoma. Metastasis of breast, gastrointestinal and genitalia tumors is also a frequent cause of pleural effusion through lymphatic spread and it is important to observe the dominant cytomorphological picture of pleural effusion in adenocarcinoma metastasis.

Objective: To determine the cytomorphology of adenocarcinoma metastasis in pleural effusion fluid

Material and Methods: Cytomorphological observations were performed on pleural effusion cytology slides consisting of 36 samples to determine the dominant cytomorphology. All characteristic data are obtained through medical records and pathology archives. Statistical analysis is descriptive with cross sectional approach.

Result: Most of the patient were diagnosed at the age of 55-64 years with female dominance and the origin of all metastases from lung adenocarcinoma. The most common cytomorphology of long adenocarcinoma metastasis in pleural effusion fluid is the hyperchromatic nucleus, pleomorphic nucleus and increased N/C ratio and subsequent sequences are irregular core membrane, macronucleoli, acinar, perinuclear vacuolation, cell ball, binucleated, uniform cell population, eccentric nucleus, papillary formation, berry contour and the least is cell in cell.

Conclusion: The results of this study have various similarities with previous studies, but further examination and research are needed for better results.

Keywords: Pleura effusion, adenocarcinoma, pulmonary adenocarcinoma, cytomorphology

1. Introduction

Pleural effusion due to malignancy is a common cause of mortality and morbidity in patients with pulmonary carcinoma. The incidence of pleural effusion due to malignancy can be estimated based on existing data which is about 15% of all malignancies. Postmortem studies conducted in the United States get pleural effusion due to malignancy of about 15% of the 191 cases of malignancy studied. Of the cases of deaths due to malignancy per year in the United States found pleural effusion due to 83,000 malignancy out of 656,500 cases of cancer. In the Anatomical Pathology Laboratory, RSUP Persahabatan Jakarta also found 50-60% pleural effusion caused by metastatic lung and breast tumors, 25% due to other malignancies, for example, gastrointestinal and genitourinary cancers and 7-15% unknown to the primary tumor. [1,2,3]

According to research conducted through medical record data at Persahabatan Hospital Jakarta in 2010-2011, it was found that pleural effusion was the most common cause of death in lung cancer patients, which was around 19.8% because the occurrence of pleural effusions indicated that lung cancer was already in its final stage so the prognosis bad and cause death. At Dr. Hospital Pirngadi Medan found malignant pleural effusion 24% of all cases of exudative pleural effusion that occurred within 3 years (1994-1997). While in Dr. Sutomo Hospital Surabaya in 1999 the incidence of pleural effusion due to malignancy was 27.23%. [3,4,5]

Lung cancer is the second most common cancer in the world. An estimated 1.2 million new cases and 1.2 million died in 2000 in the United States. About 52% of new cases are in developing countries. Pulmonary carcinoma three times more in men than women and is the most common cause of malignant pleural effusion. In developed countries such as the United States the incidence of pleural effusion due to pulmonary carcinoma has been reported in 641 cases from 1,783 patients with pulmonary carcinoma. In the UK the incidence rate reaches

40,000 / year. In other developing countries reported incidents have increased rapidly, among others, due to excessive cigarette consumption as in China. [4,5,6]

Lung cancer most often causes malignant pleural effusion and the most common type is adenocarcinoma. Metastasis of breast, gastrointestinal and genitalia tumors is also a frequent cause of pleural effusion through lymphatic spread. Primary tumors originating from the pleura are mesotheliomas but are rarely found, if the tumor is still localized, it will not cause pleural effusion, so it is classified as a benign tumor. Conversely, if spread can cause malignant pleural effusion. [7,8]

2. Materials and Methods

We examined 36 slides of pleural effusion in the Anatomical Pathology Unit of the Medan Adam Malik General Hospital in Medan with a cross sectional approach. We collected clinical data, including age, sex and nasal metastasis, pleural effusion from medical records. Cytomorphological features of pleural effusion fluid in adenocarcinoma were evaluated by three researchers through microscopic examination of the slide in Hematoxylin and Eosin staining.

The cytology specimens stained with H & E after fixation with 95% ethanol and with dry drying fixation, were conducted by a retrospective review by the authors. Cytological slides were examined for the presence or absence of cytomorphological criteria in adenocarcinoma namely hyperchromatic nuclei, eccentric nuclei, papillae formation, nucleus pleomorphism, acinar structure, perinuclear vacuole, increased N / C ratio, cell ball, binucleated, irregular nuclei membrane, cell in cell, cell in cell, uniform cell population, dense cytoplasm, multinucleated, berry contour and macronucleoli.

3. Results

The study sample was a pleural effusion fluid cytology slide diagnosed as pulmonary adenocarcinoma metastasis at the Medan Adam Malik Central General Hospital in 2015-2017. The total sample is 36 slides that meet the inclusion criteria. The number of samples is a little caused because the slides of most cytology examinations diagnosed with adenocarcinoma metastasis were used for EGFR examination at other centers and the samples obtained were slides not taken for EGFR examination. The following are the results of the research obtained.

Based on the sex of the patient, 13 cases were found in men (36.1%) and 23 cases in women (63.9%). The age of adenocarcinoma metastatic patients in pleural effusion fluid in this study was most commonly found in the age group 51-60 years, namely as many as 17 cases (47.2%), > 60 years as many as 17 cases (47.2%) and at least found in age group 41-50 years, that is as many as 2 cases (5.6%), with the average age of patients is 61.92 years. The origin of adenocarcinoma metastasis in pleural effusion fluid is pulmonary adenocarcinoma in 36 cases (100%) (Table 1).

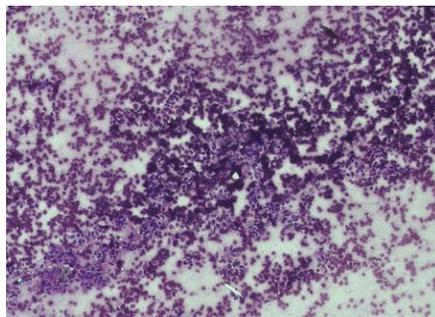
Table 1. Distribution of lung adenocarcinoma metastases based on age, sex and origin of metastasis.

Variable	Total (n)	Percentage (%)
Sex		
Man	13	36,1
Woman	23	63,9
Age		
0-44	0	0
45-54	2	5,5
55-64	27	75
≥65	7	19,5
Metastases		
Lung adenocarcinoma	36	100
Breast carcinoma	0	0
Gastrointestinal carcinoma	0	0
Ovarium carcinoma	0	0
Total	36	100

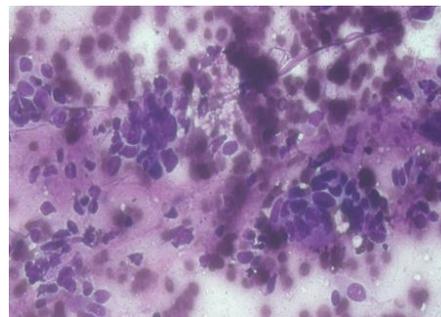
The most common cytomorphology of adenocarcinoma metastasis in pleural effusion fluid is hyperchromatic nuclei, nuclei pleomorphism and increased n / c ratio of 36 cases (100%) followed by irregular nuclei membranes and macronucleoli in 32 cases (88.9%), accounting for 29 cases (80.6%), 24 cases of perinuclear vacuola (66.7%), 23 cases of cell ball (63.9%), 21 cases of binucleated (58.3%), and 19 cases of eccentric nuclei and uniform cell population (52.8%), papillary formation of 10 cases (27.8%), dense cytoplasm and berry contour with 9 cases (25%) and cell in cell as many as 7 cases (19.4%) (Table 2).

Table 2. Cytomorphological distribution of adenocarcinoma metastasis in fluid pleural effusion

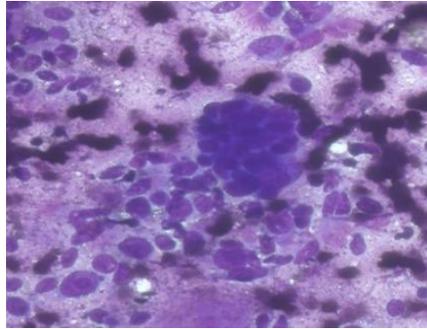
Cytomorfology	Total (n)	Percentage (%)
Structure appearance		
Acinar	29	80,6
cell ball	23	63,9
Uniform cell papulation	19	52,8
Papillary formation	10	27,8
Berry contour	9	25,0
cell in cell	7	19,4
cell appaerance		
Hyperchromatic nuclei	36	100
Nuclei pleomorphism	36	100
Increased n/c ratio	36	100
Irregular nuclei membran	32	88,9
Macronucleoli	32	88,9
Perinuclear vacuolation	24	66,7
Binucleated	21	58,3
Eccentric nuclei	19	52,8
Dense cytoplasma	9	25,0



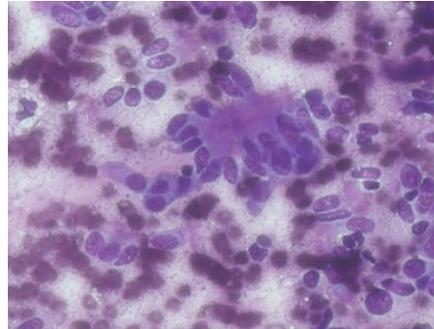
Gambar 1. *Papillary formation*



Gambar 2. *Pleomorphism nuclei, Irregular nuclei membrane, increased N/C ratio dan hyperchromatic nuclei*



Gambar 3. Cell ball dan macronucleoli



Gambar 4. Struktur acinar, inti sel binucleated

4. Discussion

In this study, sufferers of pleural effusion originating from pulmonary adenocarcinoma metastasis recorded in the medical record of the Anatomical Pathology Unit of H. Adam Malik Hospital Medan from 2015-2017 were 36 samples that met the inclusion criteria. Of the 36 samples of pulmonary adenocarcinoma metastatic patients, women were more than men (Table 4.1). This data is in accordance with the study of Makinen, et al (2017) and Yovi, et al (2017) and WHO (2015) also state that pulmonary adenocarcinoma is more common in non-smoking women than men. [6,7]

Age grouping of pulmonary adenocarcinoma metastatic patients in pleural effusion fluid is made into 4 groups. This is in accordance with the grouping of pulmonary adenocarcinoma patients from GLOBOCAN in the United States. In 2002, data based on age incidence worldwide had 5% of lung cancer cases at the age of 0 to 44 years, 14% in the age group 45 to 54 years, 24% at the age of 55 to 64 years and 55% at the age of more than 65 years.48 These results are different from those obtained in this study. In this study the most adenocarcinoma sufferers at the age of 55 to 64 years as many as 27 cases (75%), and the least in the age group 45 to 54 years as many as 2 cases (5.5%). This difference may be due to differences in smoking status in the two different countries. The results of this study are also the same as those conducted by Makinen, et al (2017) which states that the age group of patients is at most > 65 years as many as 61 cases (54.5%) and the least in patients with pulmonary adenocarcinoma who are less than < 65 years as many as 51 cases (45.5%). This statement is supported by WHO (2015) which states that the incidence of lung cancer occurs at the age of 54-75 years. [9]

The origin of adenocarcinoma metastasis in pleural effusion fluid for this study came from pulmonary adenocarcinoma in 36 cases (100%) from 2015-2017 (table 4.3). This is due to the majority of cases of pleural effusion in RSUP H. Adam Malik EGFR examination was done so that the pleural effusion cytology fluid samples were obtained slightly. This data is obtained from the patient's medical record and also does not carry out further examinations to determine the origin or location of metastases, for example IHC examination to determine the primer of adenocarcinoma. This result is also in accordance with Yovi's research at Arifin Ahmad Pekanbaru Hospital in 2017 where the most common metastatic origin of pleural effusion patients was pulmonary adenocarcinoma (42.9%) .7 According to Koss (2016), pulmonary adenocarcinoma is the most common type of tumor found in effusion and this is related to the location of pulmonary adenocarcinoma originating from the peripheral part of the lung adjacent to the pleura. [11]

The theory of cytological assessment of pleural effusion is routinely used in determining the diagnosis, determining prognosis and in determining the management of malignant neoplasms. Most patients with malignant pleural effusion are known to have a history known before, but sometimes a history of unknown disease and effusion is one sign of a malignancy. Accurate initial diagnosis will guide adequate therapy and better life expectancy from patients. Overlapping features can complicate cytopathological adenocarcinoma diagnosis. [6,10,11]

According to Koss (2016), adenocarcinoma originating from the main bronchi has three structures, namely papillary, tubulopapillary and acinar. Images that form a gland-like structure with a central lumen or called acinar are very helpful in identifying adenocarcinoma. Papillary images are cells that make up clusters around the lumen, form cell junctions and often contain deposits of central collagen as a supporting structure. These cell images often appear in the form of clusters or three-dimensional papillaries or round configurations with overlapping tumor cells. Usually a three-dimensional picture consists of several layers of cells and can form a picture of a cell ball or form a gland-like structure with a central lumen called acinar and this is very helpful in identifying adenocarcinoma. Many malignant tumors, especially adenocarcinomas form a picture of cells consisting of a large number of cells. The description of these structures is seen in the cytology of pleural effusion. [6,10,11]

In this study, there were 29 acinar structures found in adenocarcinoma found (80.6%) and this was in accordance with the study of Cakir E et al. (2008) which found an acinar structure in adenocarcinoma of 62.5% of all cases. checked. According to Koss (2016), tumors originating from the gland usually produce cell groups in serous fluid with central luminal or pseudoacinar and this is a predictor of adenocarcinoma.10 The picture of cell ball in this study was 23 cases (63.9%) and this result was appropriate with the study of Cakir E et al. (2008), which obtained a picture of cell ball in 45% of all cases, both of these studies obtained a picture of cell ball in many samples. Kho-Dufin et al. (2008) stated that the presence of many groups of ball cells coupled with a ratio of cytoplasm with a low nucleus is a very helpful illustration of identification of pulmonary adenocarcinoma. [12]

In this study, uniform cell population was found in 19 cases (52.8%), this result is different from the study of Cakir E et al (2008), which is as much as 35% of all cases. This difference may be due to this picture not found in all cases of adenocarcinoma. According to Koss (2016), one third of the cases of adenocarcinoma also display an image of uniform cell population, so that the meaning of this picture can be used as a predictor of adenocarcinoma.10 The structure of the papillary formation in this study was 10 cases (27.8%). This is very different from the research of Cakir E et al. (2008) and Erika et al. (2003) who obtained the papillary formation structure of 90% and 6% of all cases.9,47 This difference may occur due to differences in the type of adenocarcinoma in this study there was no known type of adenocarcinoma, the structure of papillary formation was found in papillary adenocarcinoma types. According to WHO (2015) papillary formation is found in the cytomorphology of pulmonary adenocarcinoma. Berry contour in this study was found in 9 cases (25.0%), in contrast to the Cakir E et al. (2009) study found in 62.5% of all cases. According to Ali et al., (2013) berry contour is a collection of cells that are found in many cases of malignant mesothelioma.48 Bonito et al. Also indicated a picture of berry border as an important criterion in malignant mesothelioma.49 Cell-cell images were found in 7 cases (19.4 %), this is in line with the research of Erika et al. (2013) which stated that cell in cell was found in 5 cases out of 18 cases of pulmonary adenocarcinoma that were examined while in the study of Cakir E et al. (2008) it was found 32.5% of all cases. Cell in cell images are commonly found in mesothelioma. [11,13]

According to some literature, the nucleus of large pulmonary adenocarcinoma with fine granular chromatin and is usually mild to moderate hyperchromatic, often with multiple or multiple nucleoli, irregular nuclei membranes and sometimes accompanied by nuclear holes. In multinucleated pulmonary adenocarcinomas are often encountered and rarely occurs in core picnosis. The description of the core perinuclear vacuolation indicates that water content and fat storage can also cause vacuole formation. The viability of these cells is unknown, although a broad vacuole may be a manifestation of the death of cytoplasmic cells that are few or dense cancer cells and are also sometimes found in the presence of vacuola which can be used as a feature for malignant cell nuclei. Adenocarcinoma is a mucus producer that can produce tumor cells with a larger vacuole mucin often appear to push the nucleus to one side, sometimes causing the nucleus to exit the cell. [6,10,11]

In this study, the most common cytomorphology of adenocarcinoma metastatic cells in pleural effusion fluid was hyperchromatic nuclei, nuclei pleomorphism and increased n / c ratio in 36 cases (100%). The results of the study by Cakir E et al, in 2008, of 40 cases of pulmonary adenocarcinoma which had a nucleus of pleomorphism of 85% and Erika et al (2013) stated that nuclei pleomorphism in pulmonary adenocarcinoma was 11 cases out of 18 cases (61%). The three core images are a sign of malignancy. Irregular membrane nuclei and macronucleoli in 32 cases (88.9%). The results of the study by Cakir E et al. (2008) state that irregular nuclei membranes (50%) and macronucleoli (15%) were found in cytology of pulmonary adenocarcinoma pleural effusion but the results of this

study are different from those of Erika et al (2013) who found macronucleoli 7 of 18 cases (38.8%). According to Orell (2012), macronucleoli and irregular nuclei membranes are the core images found in adenocarcinoma. The presence of the nucleoli is a diagnostic important capital in the introduction of cancer cells in effusions, but the enlarged nucleoli often occurs in mesothelial cells. [11]

In this study, the core picture of perinuclear vacuolation was 24 cases (66.7%) and this is consistent with the study of Cakir E et al. (2009) who found perinuclear vacuola in pulmonary adenocarcinoma in 62.5% of all cases. Perinuclear vacuola is a predictor of pulmonary adenocarcinoma. Binucleated as many as 21 cases (58.3%) and this is in line with the study of Cakir E et al. (2009) who found binucleated pulmonary adenocarcinoma of 57.5%. According to Koss (2016), cytology of pulmonary adenocarcinoma can be seen as a picture of binucleated nuclei because this picture shows a malignancy. The core picture of eccentric nuclei in this study was found in 19 cases (52.8%). This is very different from the Cakir E et al. (2009) study, which is 87.5% of all cases and this is in accordance with WHO which says that one of the cytomorphology of pulmonary adenocarcinoma is the location of the core at the edge or also called eccentric nuclei. In this study cytoplasm was found in 9 cases (25%) and in the Cakir E et al. (2009) study found dense cytoplasm as much as 55%, according to Ali et al (2012) dense cytoplasm was rarely found in cytology of pulmonary adenocarcinoma. [9,14]

This study has several disadvantages, namely the sample obtained is a bit because the pleural effusion slides diagnosed with adenocarcinoma are mostly EGFR examination in Jakarta, so the samples obtained are the remaining samples that were not taken for EGFR examination and after a slide review only 36 slides could cytomorphological examination. Most preparations for pleural effusion come from pulmonary doctors, clinical doctors other than lung rarely send available pleural effusions to be examined by the Anatomic Pathology Unit of H. Adam Malik General Hospital in Medan because other clinical doctors see pleural effusion usually only for tumor staging. The rest of the pleural effusion preparations examined in the study came from pulmonary doctors and based on medical record data from metastases from all the slides studied were pulmonary. It may be that a pleural effusion slide originating from metastases from non-pulmonary organs has been sent for EGFR examination.

5. Conclusion

Most patients with pulmonary adenocarcinoma metastasis in pleural effusion fluid are found in the age group 55-64 years with more female sex than men. The most common origin of metastasis in pleural effusion fluid is metastatic pulmonary adenocarcinoma. Cytomorphology of pulmonary adenocarcinoma metastasis in pleural effusion fluid is the most depicted hyperchromatic nuclei, nuclei pleomorphism and increased n / c ratio. The next most sequence is irregular nuclei membrane, macronucleoli, acinar structure, perinuclear vacuolation, cell ball, binucleated, uniform cell population, eccentric nuclei, papillary formation, berry contour and the least picture is cell in cell.

Acknowledgement

We acknowledge to all staff and residents of the Anatomical Pathology Department, University of North Sumatra / H. Adam Malik General Hospital, Medan, Indonesia for their help.

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