

Original Article

Cytological features of lung adenocarcinoma with micropapillary pattern in the pleural or pericardial effusion: analysis of 5 cases

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Abstract: Micropapillary pattern is a distinct histopathological pattern, and usually shows a high frequency of lymphatic invasion and lymph node metastases. This pattern is also reported in lung adenocarcinoma, however, only one cytological report of lung adenocarcinoma with micropapillary pattern has been reported. In this study, we analyzed the cytological features of this type of carcinoma in the pleural or pericardial effusion. This study was comprised of 5 consecutive cases of lung adenocarcinoma with micropapillary pattern, in which the tumor cells were present in the pleural or pericardial effusion and whose diagnoses were histopathologically confirmed. The characteristic cytological findings in the pleural or pericardial effusion were as follows: i) tightly cohesive small nests of tumor cells showing papillary structure without fibrovascular core, ii) these nests were comprised of approximately 5-20 tumor cells, iii) cauliflower-like and acinar-like structures were also observed, iv) intracytoplasmic vacuoles were observed in 40% of the cases, and v) the neoplastic cells had large round to oval nuclei containing coarse chromatin and occasional conspicuous nucleoli. It has been reported that the presence of micropapillary structure and intracytoplasmic vacuolation are also characteristic cytological features of micropapillary carcinoma of the urinary bladder, therefore, they are thought to be common cytological features of carcinomas with micropapillary pattern. Consequently, detection of these features can lead to a cytodiagnosis of lung adenocarcinoma with micropapillary pattern in the pleural or pericardial effusion. Recognition of these features is important because this type of tumor shows an aggressive clinical course.

Keywords: Lung adenocarcinoma, micropapillary pattern, pleural effusion, cytology

Introduction

Micropapillary pattern is a distinct histopathological pattern, which is characterized by the presence of small nests of carcinoma cells surrounded by clear empty spaces in the invasive portion with delicate and filiform processes on the surface [1, 2]. The neoplastic cells showing this pattern characteristically display a reverse polarity growth, whereby the apical pole of the cells faces the stroma and not the luminal surface (inside-out pattern) [1, 2]. This pattern has been reported in various anatomical sites, including the breast, salivary gland, stomach, colorectum, urinary bladder, and ovary [1, 3-10], and usually shows a high frequency of lymphatic invasion and lymph node metastases [1].

Amin *et al.* first reported lung adenocarcinomas with micropapillary pattern in 2002 [11]. Since then, several clinicopathological studies have demonstrated that this type of tumor, as well as

those in other organs, shows an aggressive clinical course [12, 13]. Further, only limited reports of the cytological features of lung adenocarcinoma with micropapillary pattern have been documented [14-16], and only one report regarding the cytological features of invasive micropapillary carcinoma of the lung detected in the pleural effusion has been documented [17]. In this report, we analyzed the cytological features of a series of lung adenocarcinoma with micropapillary pattern present in the pleural or pericardial effusion.

Materials and methods

Case selection

This study was comprised of 5 consecutive cases of lung adenocarcinoma with micropapillary pattern, in which the tumor cells were present in the pleural or pericardial effusion and whose diagnoses were histopathologically con-

Micropapillary adenocarcinoma in the pleural effusion

Table 1. Clinicopathological and cytopathological features of lung adenocarcinoma with micropapillary pattern

Case No.	Clinical features			Cytological features					
	Age	Gender	Source	Background	Number of tumor cells	Cellular arrangement	Cell size	Cytoplasmic vacuoles	Metastasis
1	69	Male	Pleural effusion	Hemorrhagic	Few	Cohesive nests	Large	-	Lymph nodes
2	45	Male	Pleural effusion	Hemorrhagic	Few	Micropapillary	Large	-	Lymph nodes
3	72	Male	Pericardial effusion	Necrotic	Abundant	Micropapillary and single cells	Large	+	Lymph nodes
4	76	Male	Pleural effusion	Necrotic	Abundant	Micropapillary	Large	+	Lymph nodes
5	75	Female	Pericardial effusion	Necrotic	Abundant	Micropapillary	Large	-	Skin and bone

firmed collected between 2009 and 2013 at our hospital.

Cytological analyses of the pleural and pericardial effusions

Pleural or pericardial effusion specimens from patients diagnosed histopathologically with lung adenocarcinoma with micropapillary pattern were retrieved. The cytological specimens were composed of pleural effusion from 3 cases (Cases 1, 2, and 4) and pericardial effusion from 2 cases (Cases 3 and 5). These specimens were Papanicolaou-stained and analyzed for cytological features, including background, number of neoplastic cells, cellular arrangement, cell shape and size, intracytoplasmic vacuoles, and nuclear features.

Histopathological analysis of the lung adenocarcinoma

Tissues from the biopsy or surgical resection were fixed with formalin, embedded in paraffin, and stained with hematoxylin and eosin.

Immunohistochemical and immunocytochemical analyses

Immunohistochemical and immunocytochemical stainings were performed using an autostainer (Benchmark XT system, Ventana Medical System, Tucson, AZ, USA) by the same method as previously reported [18-22]. The mouse monoclonal primary antibody for epithelial membrane antigen (EMA) (clone: GP1.4, Novocastra Laboratories, Ltd., Newcastle upon Tyne, UK) was used.

Results

Patients

Table 1 summarizes the clinical features of five cases of lung adenocarcinoma with micropapillary pattern. Four cases were male, and the remaining case was female. The median age of the patients was 67.4 years (range from 45 to

76 years). All patients had metastatic lesions (lymph nodes in 4 cases, and skin and bone in the remaining case).

Cytological characteristics

Table 1 summarizes the cytological features of 5 cases of lung adenocarcinoma with micropapillary pattern. The background was necrotic or hemorrhagic. The number of tumor cells was abundant in three cases. The characteristic micropapillary feature, which was characterized cytopathologically by the presence of tightly cohesive small nests of tumor cells showing papillary structure without fibrovascular core, was observed in four cases (**Figure 1A-D**). These cohesive nests were comprised of approximately 5-20 neoplastic cells (**Figure 1A, 1B**). Cauliflower-like structure with nuclei located peripherally and small acinar-like structure were also observed (**Figure 1B**). Moreover, three dimensional cohesive nests were also present (**Figure 1C**). The remaining one case (Case 1) had no micropapillary tumor cell nests although a few cohesive small nests of neoplastic cells were present. The size of these neoplastic cells was large, and they had large round to oval nuclei containing coarse chromatin and occasional conspicuous nucleoli (**Figure 1B, 1D**). Moreover, intracytoplasmic vacuolation was observed in two of five cases (**Figure 1D**).

Immunocytochemical findings

EMA was expressed in the cell membrane of the peripheral portion of the neoplastic cells, but not in the inner side (**Figure 1E**), which represents the “inside-out pattern”.

Histopathological and immunohistochemical characteristics

All five cases had characteristic micropapillary growth pattern (**Figure 2**), and the immunostaining for EMA clearly showed the “inside-out pattern”.

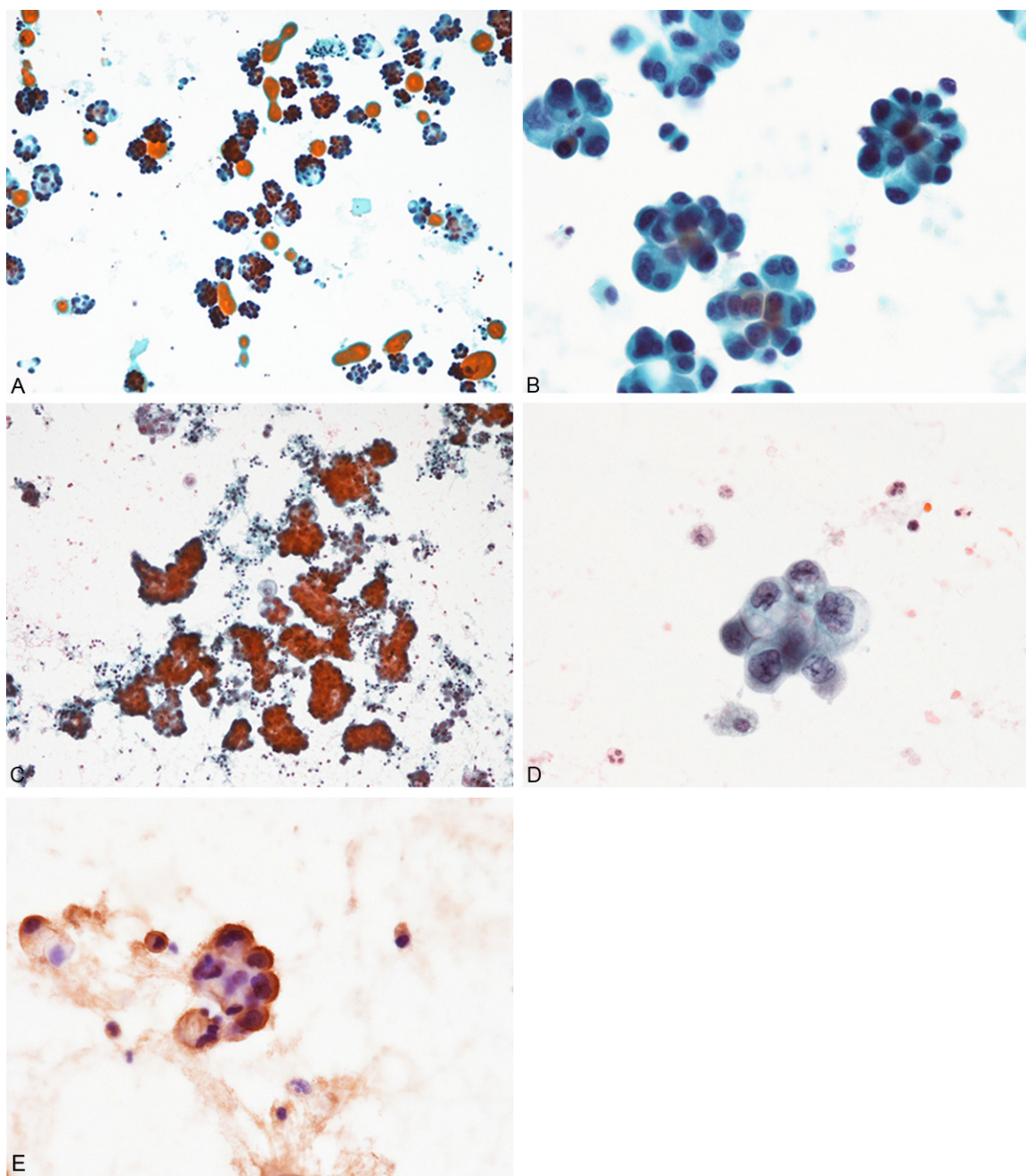


Figure 1. Cytological and immunocytochemical features of lung adenocarcinoma with micropapillary pattern in the pericardial (Case 5) or pleural effusion (Case 4). A: Abundant tightly cohesive small nests composed of approximately 5-20 neoplastic cells (Case 5) (Papanicolaou staining, x 100). B: The neoplastic cells show papillary structure without fibrovascular core, cauliflower-like or small acinar-like structures. The neoplastic cells have large round to oval nuclei with coarse chromatin, and the nuclei is located at the periphery of the neoplastic cells (Case 5) (Papanicolaou staining, x 400). C: Three dimensional cohesive tumor cell nests are also noted (Case 4) (Papanicolaou staining, x 100). D: Tumor cells have large round to oval nuclei containing coarse chromatin. Intracytoplasmic vacuoles are also noted (Case 4) (Papanicolaou staining, x 400). E: Immunostaining for epithelial membrane antigen clearly demonstrates positive reactivity in the cell membrane of the peripheral portion of the neoplastic cells (Case 4) (x 400).

Discussion

This report is the first to clarify the cytological features of lung adenocarcinoma with micro-

papillary pattern in the pleural or pericardial effusion in a case series of 5 patients, although Kuroda *et al.* reported the first cytological report of invasive micropapillary carcinoma of

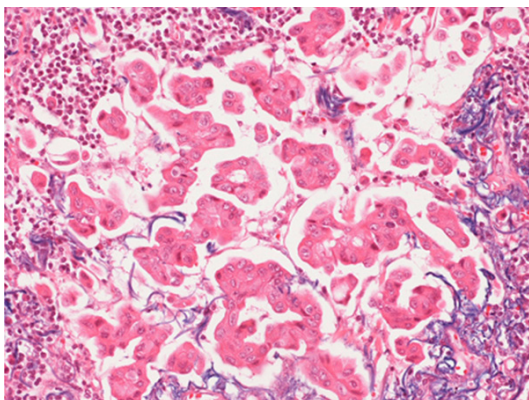


Figure 2. Histopathological feature of lung adenocarcinoma with micropapillary pattern (Case 4). Typical micropapillary pattern is noted (HE, x 200).

the lung in pleural effusion [17]. This report clearly demonstrated the following cytological findings of this type of tumor in the pleural or pericardial effusion: i) tightly cohesive small nests of tumor cells showing papillary structure without fibrovascular core, ii) these nests were comprised of approximately 5-20 tumor cells, iii) cauliflower-like and acinar-like structures were also observed, iv) intracytoplasmic vacuoles were observed in 40% of the cases, and v) the neoplastic cells had large round to oval nuclei containing coarse chromatin and occasional conspicuous nucleoli. These cytological features were fundamentally the same as those of the case reported by Kuroda *et al.* [17].

The characteristic cytological feature of lung adenocarcinoma with micropapillary pattern is the presence of tightly cohesive small nests of tumor cells showing papillary structure without fibrovascular core. This feature represents histopathological reverse polarity growth (inside-out pattern), and we first demonstrated that EMA was expressed in the cell membrane of the peripheral portion of the neoplastic cells in the cytological specimen. This finding was observed in four of 5 cases of our series (the remaining case (Case 1) had only a few tumor cells forming cohesive small nests, and no micropapillary structure was detected in the cytological specimen). The presence of micropapillary pattern in the cytological specimen of the pleural or pericardial effusion can lead to a cytodiagnosis of adenocarcinoma with micropapillary pattern.

The cytological features of carcinoma with micropapillary pattern have also been reported

in other organs, such as urinary bladder and breast [23-27]. Zhu *et al.* analyzed 23 urine specimens of micropapillary carcinoma of the urinary bladder and compared them with conventional high-grade urothelial carcinoma [24]. They concluded that the presence of micropapillae and cytoplasmic vacuoles in the neoplastic cells from the urine specimens were more frequently observed in micropapillary carcinoma compared to conventional high-grade urothelial carcinoma (81% vs 14.3% and 57.1% vs 14.3%, respectively) [24]. Kim *et al.* also analyzed the cytological features of micropapillary urothelial carcinoma of the urinary bladder and compared them to conventional high-grade urothelial carcinoma [23]. They concluded that the presence of tight papillary cell clusters and small acinar structures are more characteristic findings in micropapillary carcinoma as compared to conventional high-grade urothelial carcinoma, although cells from both tumors had vacuolated cytoplasm [23]. In these two reports, the authors stated that these cytological features, such as the presence of micropapillae, cytoplasmic vacuoles, and acinar structures, can be helpful in differentiating micropapillary urothelial carcinoma from conventional high-grade urothelial carcinoma, and moreover, early cytodiagnosis leads to correct treatment [23, 24]. The cytological features of the present case series of lung adenocarcinoma with micropapillary pattern in the pleural or pericardial effusion are fundamentally the same as those in this report [23, 24]. Therefore, these results suggest that cytodiagnosis of adenocarcinoma with micropapillary pattern is possible by examination of the pleural or pericardial effusion. Detection of this component is very important for correct treatment because lung adenocarcinoma with this pattern shows an aggressive clinical course.

Disclosure of conflict of interest

None.

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