

The Fine Needle Aspiration Cytology of a Metastatic Pulmonary Adrenocortical Carcinoma Mimicking Primary Large Cell Carcinoma of the Lung

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Adrenocortical carcinoma is a rare neoplasm and it has an invariably lethal prognosis. We report here on the fine needle aspiration cytologic findings of a solitary metastatic pulmonary adrenocortical carcinoma in a 24-year-old woman. The aspirate smears were very cellular and they were composed of a monomorphic population of large polyhedral cells with abundant granular or vacuolated cytoplasm, and the cells were predominantly singly scattered in a necrotic background. Multinucleated pleomorphic tumor cells were also found. Pleomorphic nuclei with thickened nuclear membranes were impinging on the cell membranes. Mitotic activity was occasionally seen. The cytologic findings of pleomorphic cells with microvacuolated cytoplasm and the presence of vague gland-like sheets, as well as the patient's history of undergoing adrenalectomy for primary adrenocortical carcinoma helped the pathologist reach the diagnosis of metastatic adrenocortical carcinoma. Here, we focus on the cytologic differential points of metastatic pulmonary adrenocortical carcinoma and primary pulmonary carcinoma, especially large cell carcinoma.

Key Words : Aspiration cytology; Adrenocortical carcinoma; Neoplasm metastasis; Carcinoma, large cell; Lung neoplasms

Adrenocortical carcinoma is a rare malignant neoplasm and it accounts for less than 0.05% of all malignant neoplasm with an estimated incidence of 0.5 to 2 cases per million persons/year.^{1,2} Adrenocortical carcinoma shows a bimodal age distribution with peaks in the first and fourth to fifth decades of life, but it primarily occurs in children and young adults. The patients with this disease often present with metastatic diseases.³ The most common metastatic sites are liver, lung, the retroperitoneal lymph nodes, and bone. Pulmonary metastases to the adrenal gland are much more common than primary adrenal tumors, whereas metastases to the lung are uncommon in patients with a malignant endocrine neoplasm.⁴

Fine needle aspiration cytology is usually a reliable and accurate method for making the diagnosis of pulmonary malignancy with high specificity and sensitivity and low false positive and negative rates.⁵ Yet the accuracy of cytologically subtyping non-small cell carcinomas is poor. Among them, large cell carcinomas of the lung, as defined by the World Health Organiza-

tion, are poorly differentiated tumors and more importantly, the diagnosis is that of exclusion and it is made after ruling out a component of the known entities that are frequently encountered in the lung. This entity also has a myriad of morphologic variations and virtually every known metastatic malignancy to the lung can look like a primary large cell carcinoma of the lung.

We report here on a case of metastatic pulmonary adrenocortical carcinoma that was demonstrated by fine needle aspiration cytology and we discuss the possible cytologic differential diagnoses.

CASE REPORT

Chest computed tomography (CT) revealed a solitary nodule at the left upper lobe of the lung in a 24-year-old woman (Fig. 1A). She had undergone a left adrenalectomy operation eight months previously. At that time, she had suffered from left flank



Fig. 1. (A) The chest computed tomography (CT) reveals a small nodule (arrow) at the lingular division of the upper lobe of the left lung. (B) Abdominal CT reveals a well defined, heterogeneously enhancing mass (arrow) in the left adrenal gland.

pain for the previous four days before visiting a clinic. An abdominal ultrasound scan showed an echogenic mass at the left kidney. Abdominal CT revealed a 9.0 cm-sized well defined, heterogeneous enhancing mass in the left adrenal gland (Fig. 1B). The patient underwent left radical adrenalectomy. Left upper lobectomy was done, and the patient was administered palliative chemotherapy (mitotan 15 cycles during 18 months). Nine months later, a newly developed lobulated heterogeneous mass that measured 5.6×3.8 cm was detected at the lower pole of the left kidney. Neutron therapy was done and left partial nephrectomy then followed. Three months later, the follow up CT revealed that a retroperitoneal recurrence had developed and so mass excision was done. She has had an uneventful course during the 13 months of follow up.

Cytologic findings

Aspirates were obtained from the left adrenal gland and the upper lobe of the left lung using a 20-gauge biopsy needle under computed tomographic or ultrasonic guidance. The direct smears were fixed in ethanol for Papanicolaou staining or hematoxylin and eosin stain. The cell blocks were sectioned and stained with hematoxylin and eosin.

All the smears taken via the fine needle aspiration cytology from the left upper lung mass showed highly cellular smears with abundant groups of round to polyhedral tumor cells in

abundant karyorrhectic necrotic debris (Fig. 2A). Occasionally, acinar structure-like loose-cellular clusters were also present in the aspirated lung mass. The tumor cells had finely vacuolated, abundant cytoplasm with centrally placed hyperchromatic, enlarged nuclei (Fig. 2B). The tumor cells occasionally showed spindle-shaped nuclei that were markedly increased in size, with prominent atypia. Naked nuclei were occasionally observed. Multinucleated, atypical giant cells, pyknotic cells and a high mitotic rate were also evident. The cell block preparation showed mostly single uniform cells with rare tumor clusters. The aspirates from the left adrenal mass revealed sheets or singly scattered, round-shaped tumor cells in a necrotic and bloody background (Fig. 2C). The relatively uniform sized tumor cells had an abundant amount of foamy cytoplasm and centrally located large dark nuclei with occasional prominent nucleoli (Fig. 2D). Atypical mitoses were occasionally observed. No cell clusters or rosettes were found. These cytologic findings were the same as those of the lung.

Histologic findings

The left upper lobectomy specimen was a well demarcated 1.5 cm-sized oval shaped mass (Fig. 3A). Metastatic carcinoma was found in 2 out of the 20 hilar lymph nodes. Microscopically, the oval mass was composed of sheets of atypical cells having abundant clear granular cytoplasm and enlarged hyperchromatic

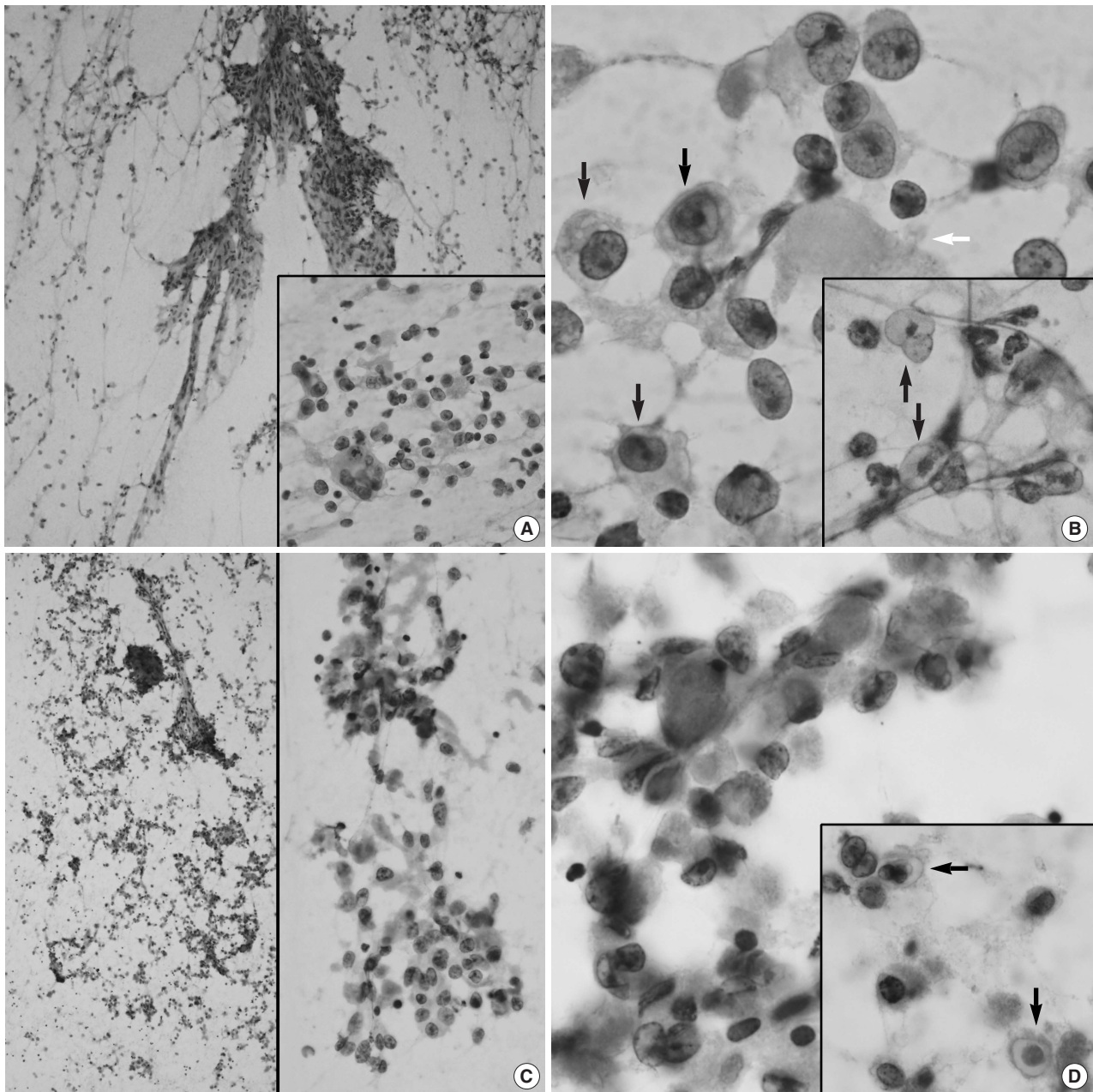


Fig. 2. (A) The cellular smear taken from the lung mass shows vague sheet-like arrangements and many singly scattered cells in a necrotic background (Papanicolaou). The inset indicating a mixed population of round cells with occasional plasmacytoid appearances and multi-nucleated cells. (B) The round tumor cells show abundant clear cytoplasm (arrows) and necrotic debris (white arrow). The inset indicates bare nuclei with popcorn-like appearances (arrows, Papanicolaou). (C) The cellular smear taken from the adrenal mass reveals many singly scattered cells (left) with a few sheets of tumor cells (right, Papanicolaou). (D) Large round tumor cells are intermixed with necrotic debris. The inset indicates the round shaped tumor cells having clear cytoplasm (arrows, Papanicolaou).

ic nuclei, similar to those of the left adrenal mass (Fig. 3B). The adrenalectomy specimen that was obtained eight months previously showed a well circumscribed oval mass measuring $9.0 \times 8.5 \times 5.0$ cm and weighing 200.0 g. The cut surface was of various colors from dark brown to yellow with marked necrosis and hemorrhage (Fig. 3C). The histological sections of the ad-

renal mass showed sheets of malignant cells separated by fine fibrous septae, and the cells displayed clear cytoplasm in areas (Fig. 3D). A higher power view showed diffuse sheets of atypical clear cells and cells with eosinophilic granular cytoplasm. The tumor showed confluent tumor necrosis, cellular pleomorphism, occasional mitoses (up to 8 per 10 high power fields) and capsu-

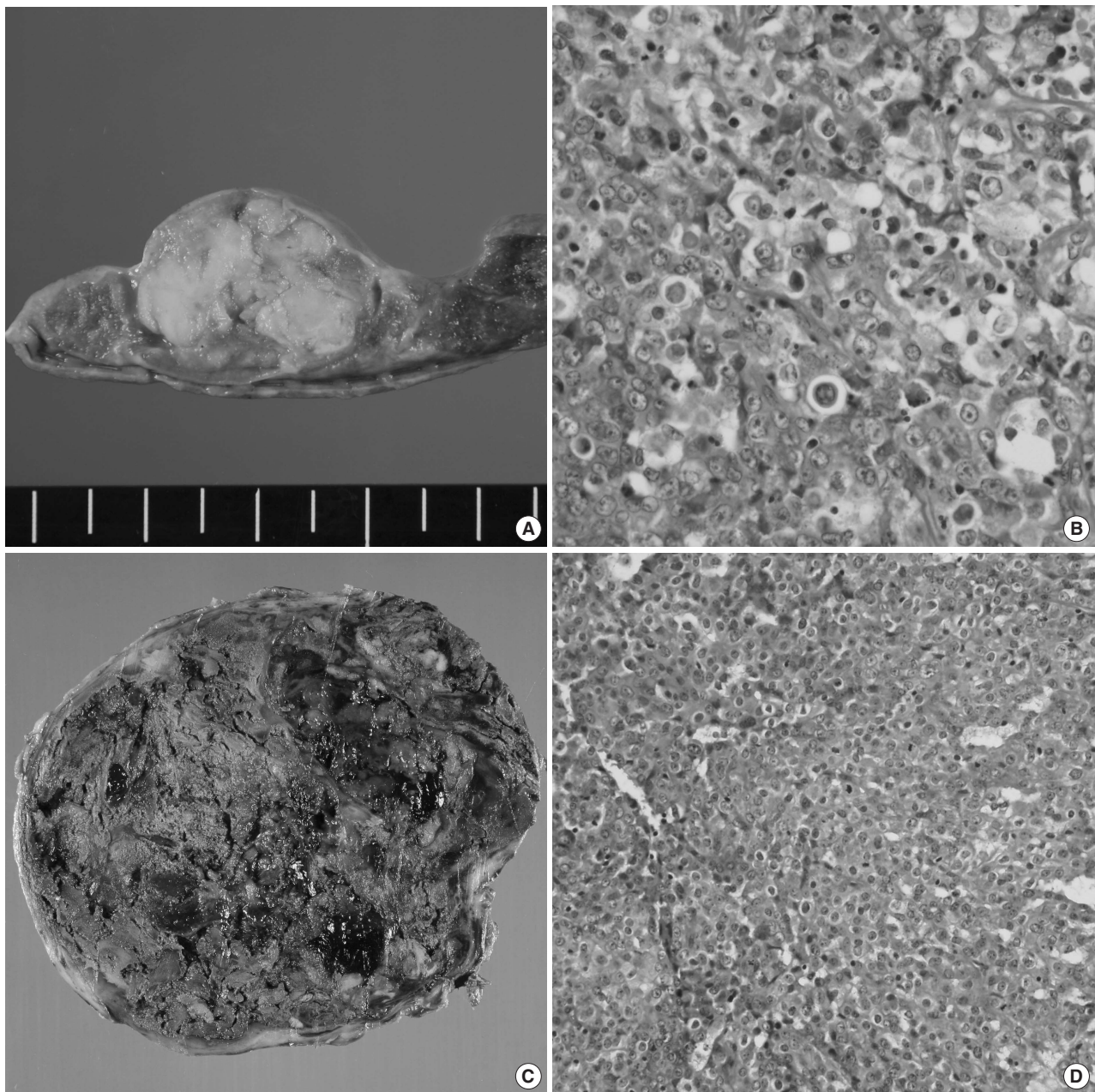


Fig. 3. (A) The gross picture of the left upper lobe shows a well demarcated solitary mass with a slightly myxoid cut surface. (B) A higher power view of the lung mass reveals diffuse sheets of tumor cells having eosinophilic granular cytoplasm and large hyperchromatic nuclei. (C) The gross picture of the left adrenalectomy specimen shows an oval shaped mass that totally replaced the entire adrenal gland with a tan-yellow cut surface and areas of hemorrhage and necrosis. (D) A higher power view of diffuse sheets of atypical clear cells and cells with eosinophilic granular cytoplasm.

lar invasion and vascular tumor thrombi.

Immunohistochemically, the tumor cells of both the lung and adrenal masses were focally positive for pancytokeratin (prediluted, AE1/AE3, Dako, Glostrup, Denmark), CD56 (1 : 100, 123C3, Dako), α -inhibin (1 : 100, BC/R1, Biocare Medical, Concord, CA, USA), Melan-A (prediluted, A103, Dako), calre-

tinin (1 : 100, DAK-Calret 1, Dako), epithelial membrane antigen (prediluted, E29, Dako) and synaptophysin (1 : 40, SY38, Dako), while they were negative for chromogranin (prediluted, DAK-A3, Dako), carcinoembryonic antigen (prediluted, II-7, Dako) and thyroid transcription factor 1 (1 : 50, 8G7G3/1, Dako).

DISCUSSION

The cytologic findings of adrenocortical carcinomas vary from case to case. Most of the cells are round to oval in shape and they often have abundant vacuolated cytoplasm that contains microvacuoles or macrovacuoles.^{6,7} Polygonal or plasmacytoid dyshesive tumor cells have well-preserved granular cytoplasm, nuclear pleomorphism, mitoses and prominent nucleoli.⁸⁻¹⁰ The tumor cells occur in tight sheets and they overlap. Monolayered clusters may show a branching pattern. Pleomorphic and large cells are also present. Ren *et al.*⁸ reviewed the cytologic features of primary and metastatic adrenocortical carcinomas, and they concluded that there is no single specific feature that allows making a definitive diagnosis of adrenocortical carcinoma. A combination of cytologic findings such as hypercellularity (70% of cases), a necrotic debris-rich background (70%), moderate to marked nuclear pleomorphism (80%), mitotic figures (90%) and prominent nucleoli (60%) are necessary to make the diagnosis. They suggested that more than three of these cytologic features helped make the cytologic diagnosis of adrenocortical carcinomas. Necrosis and/or mitosis were found in all the cases, and even in the tumors with bland-looking cytologic smears of adrenocortical carcinomas. Capsular and vascular invasion are features that are by far the most definitive indicators of malignant behavior, but they cannot be ascertained in cytology studies. Therefore, a necrotic background and high mitotic counts are characteristic cytologic features for diagnosing adrenocortical carcinoma.

The cytologic features of metastatic adrenocortical carcinomas may show a wide range of morphologic variation according to the metastatic sites. Typically, the cells of adrenocortical carcinoma are arranged in a diffuse sheet-like or trabecular pattern, but thin trabeculae with a sinusoidal architecture resembling hepatocellular carcinoma in metastatic hepatic adrenocortical carcinoma may be found on rare occasion.¹¹ A malignant tumor of the lung was clinically suspected in the present case although the patient had a history of primary adrenocortical carcinoma. However, the cytologic findings of the pulmonary mass were compatible to the histology of the primary adrenal tumor. Pulmonary metastatic adrenocortical carcinomas may show cytological similarity with the cytology of a well differentiated tumor that resembles a benign cortical lesion or a low-grade neuroendocrine tumor to a poorly differentiated pleomorphic tumor that mimics a primary poorly differentiated large cell carcinoma, metastatic malignant melanoma or high-grade sarcoma.⁸ Most of all, metastatic pulmonary adrenocortical carci-

nomas should be distinguished from primary large cell carcinoma, and the latter is characterized by large cells with prominent nucleoli and no mucin production or intercellular bridging, and primary large cell carcinoma lacks the cytologic and architectural features of small cell carcinoma and the glandular or squamous differentiation.¹² Large cell carcinoma does not have specific discriminating cytologic features, so the cytologic features are heterogeneous, like that of adrenocortical carcinoma. The cellular borders of the tumor cells are indistinct, so the cells of large cell carcinoma typically form a haphazard syncytial aggregates in a necrotic and neutrophil-rich background. Large cell carcinoma can show a dyshesive pattern with singly scattered, dispersed malignant cells. The tumor cells have markedly atypical nuclei with a prominent anisonucleosis and pleomorphism with cyanophilic, scant cytoplasm. Multinucleated giant cells and spindled forms can occasionally be seen. These cytologic features may be partly shared by adrenocortical carcinoma. However, a moderate amount of vacuolated cytoplasm and trabecular or vague glandular arrangements with rare sinusoidal architecture can distinguish adrenocortical carcinoma from primary pulmonary large cell carcinoma.

In summary, the cytological findings of primary and metastatic pulmonary adrenocortical carcinomas are basically similar. The solitary pulmonary tumor in the present case had metastasized in the hilar lymph nodes and it was adhered to the pleural surface of the lung. The cytological findings indicated a differential diagnosis of primary pulmonary large cell carcinoma because metastatic pulmonary adrenocortical carcinoma shows a wide range of cytologic features that may be occasionally shared with those of primary pulmonary large cell carcinoma, even though the presentation of this case was that of a solitary nodular lung mass in a 24-year-old woman with a documented history of adrenal cortical carcinoma. Therefore, cytopathologists should keep in mind the importance of taking a complete history and performing a proper physical examination and extensive radiological and laboratory evaluations to arrive at a correct diagnosis.

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