症例報告

CYTOLOGICAL APPROACH TO DIAGNOSIS FOR LARGE CELL NEUROENDOCRINE CARCINOMA

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Abstract : Clinical data or investigation of large cell neuroendocrine carcinoma (LCNEC) have accumulated, some of which however, can be flawed by erroneous cytological diagnosis. In this report, we present a case of LCNEC suspected of originating in the lung, and discuss cytological features or differential diagnosis. Aspiration cytology showed clusters of tumor cells with large and polymorphic nuclei and distinct nucleoli. The cytoplasm was positive for some markers for neuroendocrines, is similarly as demonstrated in histological findings of metastasis in the cervical lymph node. LCNEC rapidly develops and often reaches an advanced stage, and we have sometimes found that fine needle biopsy or cytology is the only tool for pathological suggestion or diagnosis. Therefore, it is necessary to accumulate case reports as presented here and confirm cytological features, which might help us to make an accurate diagnosis of LCNEC and to distinguish it from other neuroendocrine neoplasms including small cell carcinoma or poorly differentiated tumors.

Key words : cytology, large cell neuroendocrine carcinoma, differential diagnosis.

INTRODUCTION

Large cell neuroendocrine carcinoma (LCNEC) was produced as a new category of pulmonary neuroendocrine tumors, with is a poor prognosis similar to that of small cell carcinoma[1]. A number of studies have been counducted to clarify histopathological diagnosis for this entity[1-5] : (1) neuroendocrine appearance by microscopy including palisading, rosette like architecture; (2) large tumor cells with a low nuclear cytoplasmic ratio, polygonal shape, finely granular eosinophilic cytoplasm, coarse chromatin, and frequent nucleoli ; (3) high mitotic rate; (4) frequent tumor necrosis ; (5) neuroendocrine features by immunohistochemistry. However, cytological appearance of the tumor cells are varied and the diagnostic criteria remain undetermined. Particularly ; the differential diagnosis of LCNEC from small cell carcinoma is sometimes very difficult, therefore, it is necessary to confirm the cytological criteria for generalizing neuroendocrine tumors into the categories of small cell versus non-small cell types. We have experienced a case of LCNEC suspected of originating in the lung manifested by cervical lymphadenopathy due to metastasis and

severe pleural effusion. In this report, we demonstrat morphological or immunocytological features of tumor cells, and discuss useful and problem points in approach to diagnosis for LCNEC.

CASE REPORT

The patient was a 57-year-old man with no past history of tumor. He had suffered from swelling of the right supraclavicular and cervical lymph nodes for about a year. The size of lymph nodes in both regions had gradually increased since a few months previously. Radiological examination of the chest revealed severe bilateral pleural effusion and a solid mass mainly involved in the left lung, suggesting that tumor originating in the lung was metastasized to the regional lymph nodes. After administration, cervical lymph node biopsy and fine needle aspiration cytology of pleural effusion were performed. As shown in Fig. 1,

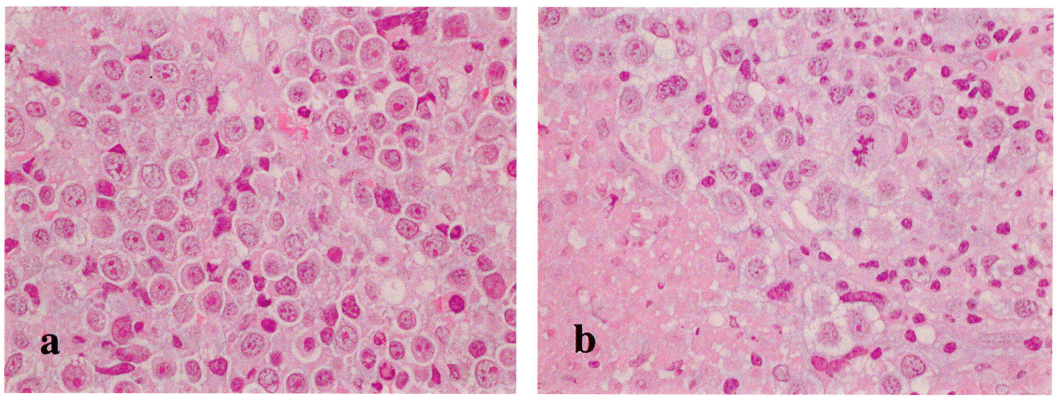

Fig. 1. Histological findings of metastatic tumors in the cervical lymph node. (H&E stain ×400)
a: The tumors cells with large and pleomorphic nuclei diffusely proliferates.
b: Necrosis and mitosis were scattered in the tumor tissue.

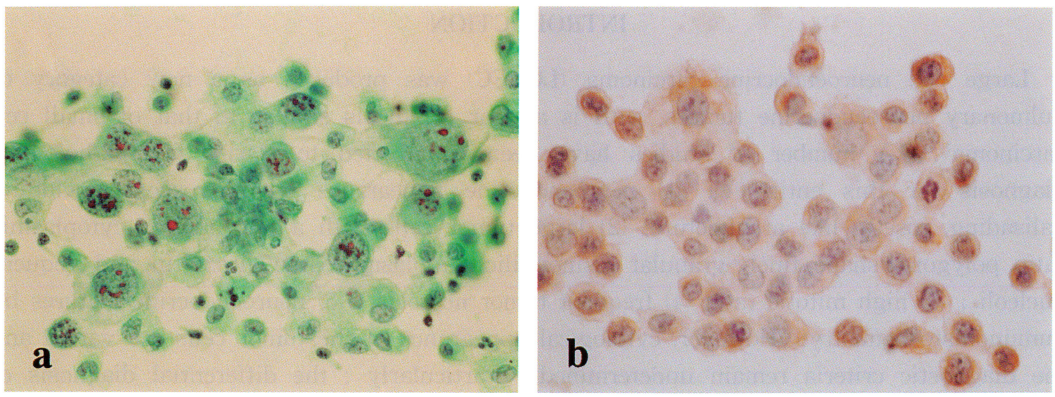

Fig. 2. Cytological findings of aspiration smear of pleural effusion.
a: Cohesive proliferation of tumor cells with large and distinct nucleoli. Chromatin pattern is coarse, and nuclear membrane is irregular. (Pap stain ×400)
b: The tumor cells are immunocytochemically positive for chromogranin-A. (×400)

atypical cells with bizarre nuclei proliferated in a diffuse or alveolar architecture, in which mitotic figures were frequently observed (35 in 10 high-power fields). The results of immunohistological examination revealed staining positive for neurospecific enolase (NSE), chromogranin-A, synaptophysin, epithelial membrane antigen (EMA), but negative for leukocyte common antigen (LCA), S-100, CD30, neural cell adhesion molecule (NCAM), cytokeratin (CK) 7, CK 20 and high molecular weight CK (34bE12). Although negative staining for NCAM, most cells were positive for three general neuroendocrine markers ; we made a diagnosis of LCNEC (metastasis in the regional lymph nodes), and ruled out malignant melanoma or hematopoietic neoplasia including anaplastic large cell lymphoma. Cytological appearance of pleural effusion smear indicated large or fusiform with a relatively finely granular cytoplasm and clear discernable nucleoli (Fig. 2A). Immunocytological examination showed that the cells were positively stained for chromogranin-A (Fig. 2B) and synaptophysin. Unfortunately, we could not accurately analyze the primary tumor lesion of the lung due to the clinically advanced stage.

DISCUSSION

LCNEC is defined as a poorly differentiated and high grade neuroendocrine tumor of non-small cell type. Although the optimal management for LCNEC remains undetermined, the clinical strategy for LCNEC is suggested to be treatment as non-small cell carcinoma, i.e. surgery for the early stages but chemo- and/or radiotherapy for advanced cases[6]. In contrast, it has been shown that chemotherapy or radiation therapy is the main strategy of treatment for small cell carcinoma except for a low stage tumor[7]. Thus, the strategy of treatment for each disease is very different, even though both LCNEC and small cell carcinoma are identified as neuroendocrinal tumors with poor prognosis ; therefore, well-defined pathological criteria are required for accurate clinical investigation. A number of reports including demonstration by Travis et al. previously showed histological criteria of this entity[1,8,9], and histological diagnosis from the primary involved lesion is not a great difficulty for pathologists. However, LCNEC is well known to rapidly develop and progress, therefore, we have sometimes found that fine needle aspiration cytology or biopsy from body cavity effusion or distant metastatic lesion is the only diagnostic tool.

To our knowledge, the cytological reviews of LCNEC were only described recently 2,10), and it is necessary to accumulate more case reports trying to make a cytological diagnosis of LCNEC, especially to distinguish it from small cell carcinoma. According to Yang et al.[2], cytological features of LCNEC are characterized by large cells with large nuclear size (3- 5 times an RBC or small lymphocytes), scant cytoplasm and distinct nucleoli, whereas small cell carcinoma features small cells with small nuclei (1-2.5 times an RBC or small lymphocyte) and indistinct or small but distinct nuclei. Also, molding of the nucleus or crush artifacts is poorly observed in LCNEC, which is an additinal differential point from small cell carcinoma. The tumor cells presented in the current report indicated all characteristic features of LCNEC. We cannot deny the possibility that only neuroendocrinal differentiated component of other types of tumors such as large cell carcinoma was metastasized to the lymph nodes. However, we consider this possibility to be slight in the present case because almost all tumor cells obtained from pleural effusion also indicated

neuroendocrines. To distinguish intermediate-cell-type small cell carcinoma of the old category from LCNEC is a very difficult. Yang et al. demonstrated that the nuclear size of LCNEC was slightly larger than that of the intermediate-cell-type small cell carcinoma (1.5 - 2.5 times as RBC)[2].

With reference to differential diagnosis, LCNEC should be distinguished not only from small cell carcinoma but also from poorly differentiated adenocarcinoma or squamous cell carcinoma[11]. Because most LCNEC may exhibit adenocarcinomatous or squamous differentiation, it is reasonable that LCNEC shows similar cytological findings to those of adenocarcinoma or squamous cell carcinoma. LCNEC shows negative staining for high molecular weight CK, whereas squamous cell carcinoma generally produces positive staining. In addition, a high percentage of adenocarcinoma shows CK7+/CK20- (or CK7-/CK20+ for colon cancer), whereas LCNEC shows negative staining for both types of CKs as demonstrated in the present case[12,13]. Although it is very difficult to distinguish LCNEC from poorly differentiated tumors completely, combinations of various immunostaining patterns may give useful clues for differential diagnosis.

REFERENCES

1) **Travis, W. D. Linnoila, R. I. Tsokos, M. G. Hitchcock, C. L. Cutler, G. B., Jr. Nieman, L. Chrousos, G. Pass, H.** and **Doppman, J.** : Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am. J. Surg. Pathol. **15** : 529-553, 1991.

2) **Yang, Y. J. Steele, C.T. Ou, X. L. Snyder, K. P.** and **Kohman, L. J.** : Diagnosis of high-grade pulmonary neuroendocrine carcinoma by fine-needle aspiration biopsy: nonsmall-cell or small-cell type? Diagn. Cytopathol. **25** : 292-300, 2001.

3) **Henderson, D. K.** and **Gerberding, J. L.** : Prophylactic zidovudine after occupational exposure to the human immunodeficiency virus: an interim analysis. J. Infect. Dis. **160** : 321-327, 1989.

4) **Warren, W. H. Memoli, V.A.** and **Gould, V. E.** : Well differentiated and small cell neuroendocrine carcinomas of the lung. Two related but distinct clinicopathologic entities. Virchows Arch. B. Cell Pathol. Incl. Mol. Pathol. **55** : 299-310, 1988.

5) **Warren, W. H. Faber, L. P.** and **Gould, V. E.** : Neuroendocrine neoplasms of the lung. A clinicopathologic update. J. Thorac. Cardiovasc. Surg. **98** : 321-332, 1989.

6) **Dresler, C. M., Ritter, J. H., Patterson, G. A., Ross, E., Bailey, M. S.** and **Wick, M. R.** : Clinical-pathologic analysis of 40 patients with large cell neuroendocrine carcinoma of the lung. Ann. Thorac. Surg. **63** : 180-185, 1997.

7) **Quoix, E. Fraser, R. Wolkove, N. Finkelstein, H.** and **Kreisman, H.** : Small cell lung cancer presenting as a solitary pulmonary nodule. Cancer **66** : 577-582, 1990.

8) **El_Naggar, A. K. Ballance, W. Karim, F. W. Ordonez, N. G. McLemore, D. Giacco, G. G.** and **Batsakis, J.G.** : Typical and atypical bronchopulmonary carcinoids. A clinicopathologic and flow cytometric study. Am. J. Clin. Pathol. **95** : 828-834, 1991.

9) **Valli, M. Fabris, G. A. Dewar, A. Chikte, S. Fisher, C. Corrin, B.** and **Sheppard, M. N.** : Atypical carcinoid tumour of the thymus: a study of eight cases. Histopathology **24** : 371-375, 1994.

10) **Wiatrowska, B. A. Krol, J.** and **Zakowski, M. F.** : Large-cell neuroendocrine carcinoma of the lung: proposed criteria for cytologic diagnosis. Diagn. Cytopathol. **24** : 58-64, 2001.

11) **Jiang, S. X. Kameya, T. Shoji, M. Dobashi, Y. Shinada, J.** and **Yoshimura, H.** : Large cell neuroendocrine

carcinoma of the lung: a histologic and immunohistochemical study of 22 cases. Am. J. Surg. Pathol. **22** : 526-537, 1998.

12) **Kende, A. I. Carr, N.J.** and **Sobin, L. H.** : Expression of cytokeratins 7 and 20 in carcinomas of the gastrointestinal tract. Histopathology **42** : 137-140, 2003.

13) **Adhikari, D. Conte, C. Eskreis, D. Urmacher, C.** and **Ellen, K.** : Combined adenocarcinoma and carcinoid tumor in atrophic gastritis. Ann. Clin. Lab. Sci. **32** : 422-427, 2002.