

Double primary non-small cell lung cancer: Pulmonary adenocarcinoma metastasizing into a synchronous typical carcinoid

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Citation

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Abstract

Metastases of tumors within a secondary tumor are rare. Here we report on a 65-year-old female patient with an advanced pulmonary adenocarcinoma. Histopathological examination revealed a synchronous typical carcinoid of the lung that included metastatic cell populations of a pulmonary adenocarcinoma. Concerning the lung, this is the first report of an adenocarcinoma metastasizing into a carcinoid.

CASE REPORT

Initially, the 65-year-old female patient was referred to hospital after a routine examination following a tick bite and coincidentally, x-ray radiographs revealed pulmonary masses in the upper and lower lobe of the right lung. Since images of computed tomography scans raised the suspicion of malignancy, surgical resection was planned. On admission to our hospital, the patient reported about a dry cough that had persisted for two months. She reported no further relevant diseases and her past medical history was negative for smoking and other lung cancer risk factors. Physical examination revealed no other significant pathological findings.

Preoperative cardiopulmonary function tests and blood oxygen levels were normal except for a sinus tachycardia up to 140 bpm. Perfusion scintigraphy of the lungs revealed a centrally located tumor in the right lung with a normal perfusion of the other lung areas. Since bronchoscopy indicated a tumour infiltration close to the right main bronchus, a pneumonectomy of the right lung was planned

Operation revealed a large tumour with a diameter of 4 cm arising from segment 2 and extending to segment 6, with infiltration into the parietal pleura. The tumor masses compressed the bronchus of the upper and middle pulmonary lobe. A pericardial infiltration of the tumour was excluded

by intrapericardial exploration. Therefore, a pneumonectomy of the right lung was carried out with a transpericardial amputation of the pulmonary artery. Dissection of the lymph nodes required tangential resection of the esophagus due to tumor-infiltrated lymph nodes infiltrating the esophageal musculature. Intraoperative histopathological diagnosis confirmed affection of the lymph nodes from the upper mediastinum. The post-operative history was uneventful and the patient was discharged from hospital 15 days after the operation.

Histopathological analysis revealed a mixed-type pulmonary adenocarcinoma (TNM: pT4, pN3, pM1, L1, GII-III). The tumor was characterized by papillary formations, partially with bronchiolo-alveolar, solid or trabecular, and partially mucinous differentiation. There were lymphatic invasions and 25 of 28 resected lymph nodes were tumor positive. Additionally, besides the adenocarcinoma in the upper and lower right lobe, a 1.2 cm nodule in the upper right pulmonary lobe with different morphology was evident. The medium-sized cells with elliptical nuclei showed a solid growth pattern, representing a typical carcinoid tumor. In the periphery of the carcinoid, a small area with similar morphology as the diagnosed adenocarcinoma was detected. To reveal the entity of these cells, further diagnostics were carried out following conventional immunohistochemical staining against carcinoembryonic antigen (CEA), thyroid

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transcription factor 1 (TTF-1), CD44V6, neuron-specific enolase (NSE), synaptophysin (SYN), chromogranin A (ChromA), neural cell adhesion molecule (N-CAM; CD56), and cytokeratins AE 1+3. The results of the staining were evaluated by at least two pathologists and are demonstrated in Table 1. Taken together, Immunohistochemistry confirmed the tumor as a typical carcinoid according to the criteria of the WHO (morphology, mitotic index, absence of necrosis), showing intratumoral metastatic formations of the adenocarcinoma expressing the same tissue antigens as the primary masses (Tab. 1). Since adenocarcinomas in female non-smokers are sometimes related to mutations in the epidermal growth factor receptor (EGFR), a specific screening for the exons 18, 19, 20, and 21 of the EGFR gene was performed as described previously [1]. The patient was found not to contain any mutations in the EGFR gene.

Figure 1

Figure 1: PAS-reaction and immunohistochemistry of the typical carcinoid. Area of the intratumoral metastases of the adenocarcinoma. A: PAS-reaction demonstrating the different morphology of the adenocarcinoma (central) and the surrounding carcinoid. B: MIB1 shows the high mitotic index of the adenocarcinoma whereas positive immunohistochemical signals are only rarely seen in the surrounding carcinoid tissue. C: Synaptophysin is exclusively expressed by the typical carcinoid whereas no immunohistochemical staining is seen in the adenocarcinoma tissue. D: In contrast, CK18 is expressed by the adenocarcinoma and not by the carcinoid. (Primary magnification: 5x).

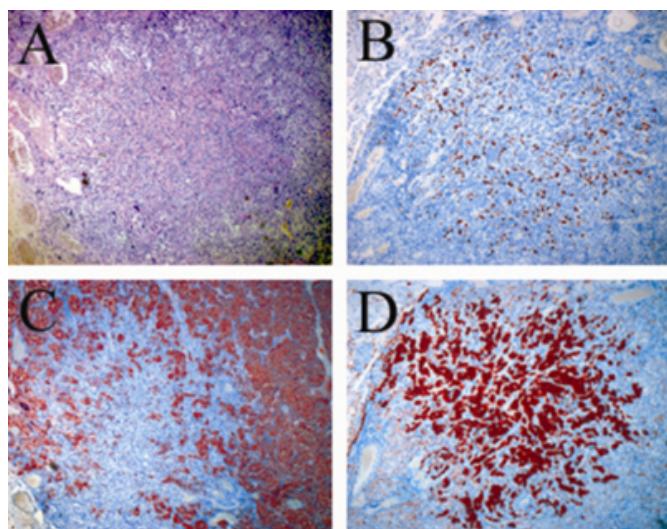


Figure 2

Table 1: Results of the immunohistochemical staining of the synchronous adenocarcinoma and the typical carcinoid. carcinoembryonic antigen (CEA), thyroid transcription factor 1 (TTF-1), CD44V6, neuron-specific enolase (NSE), Synaptophysin (SYN), Chromogranin A (ChromA), neural cell adhesion molecule (N-CAM; CD56), cytokeratins AE 1+3.

Antigen	CEA	TTF-1	CD44V6	NSE	SYN	ChromA	CD56	AE1/3
Adeno-carcinoma	+++	++	++	-	-	-	-	++
Carcinoid	-	-	-	+++	+++	-	++	-
Metastases inside the carcinoid	+++	++	++	-	-	-	-	++

DISCUSSION

Here we report on a patient with a pulmonary mixed-type adenocarcinoma in the upper and lower lobe of the right lung including lymphangiosis and lymph node metastases (TNM: pT4, pN3, pM1, L1, GII-III). In addition to these tumor masses, a typical synchronous carcinoid was evident in the right upper lobe, which contained metastases of the diagnosed adenocarcinoma. This is the first report of a pulmonary adenocarcinoma metastasizing into a synchronous typical carcinoid.

Surgically treated patients with lung carcinomas have a 1% to 5% risk per year of developing a second, metachronous primary tumor [2]. However, the development of synchronous lung tumors is an uncommon event [3]. Within the range of neuroendocrine tumors of the lung, the combination of squamous, adeno-, large cell and pleomorphic carcinoma can be found with small cell carcinoma and large cell neuroendocrine carcinoma, but is exceptional with typical and atypical carcinoids and there are only few reports about combined tumors of the lung with carcinoid and adenocarcinoma features [4, 5]. Although cases of synchronous adenocarcinomas and carcinoids are frequently described in other tissues, e.g. the digestive system, the synchronous occurrence of these two entities in the lungs is exceedingly rare [6, 7].

Combination chemotherapy remains the standard treatment following surgical resection of non-small cell lung cancer. However, the median survival with these regimens is only 8 to 10 months [8]. Survival data concerning patients with synchronous non-small cell lung cancers are limited. Kaplan-Meier analysis of a small series indicates that prognosis may not be dismal if both tumors are resectable

and the tumor stage is I or II [9]. However, to achieve an optimal outcome for the patient and to avoid up-staging assuming metastases from one tumor, it is important to be aware of the possibility of synchronous cancers.

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References

1. Meister M, Schirmacher P, Dienemann H, Mechttersheimer G, Schnabel PA, Kern MA, Herpel E, Xu EC, Muley T, Thomas M, Rieker RJ. Mutational status of the epidermal growth factor receptor (EGFR) gene in thymomas and thymic carcinomas. *Cancer Lett* 2007;248:186-191.
2. Jemal A, Thomas A, Murray T. Cancer statistics. *CA Cancer J Clin* 2002;52:23-45.
3. Flynn MJ, Rassl D, El Shahirna A, Higgins B, Barnard S. Metachronous and synchronous lung tumours: Five malignant lung pathologies in 1 patient during 7 years. *Ann Thorac Surg* 2004;78:2154-2155.
4. Sen F, Borczuk AC. Combined carcinoid tumour of the lung: a combination of carcinoid and adenocarcinoma. *Lung Cancer* 1998;21:53-58.
5. Cavazza A, Toffanetti R, Ferrari G, Piana S, Putrino I, Gardini G. Combined neoplasia of the lung: description of a case of adenocarcinoma mixed with typical carcinoid. *Pathologica* 2001;93:216-220.
6. Jung-Legg Y, McGowan SE, Sweeney KG, Zitzman JL, Pugatch RD. Synchronous triple malignant tumors of the lung. A case report of bronchial carcinoid, small cell carcinoma, and adenocarcinoma of the right lung. *Am J Clin Pathol* 1986;85:96-101.
7. Yano K, Yokoi K, Matsuguma H, Anraku M, Kondo T, Kamiyama Y, Mori K, Igarashi S. Synchronous tumors consisted of bronchial carcinoid and adenocarcinoma of the lung. *Kyobu Geka* 2002;55:457-460.
8. Martin P, Kelly C.M.A., Carney D. Epidermal growth factor receptor-targeted agents for lung cancer. *Cancer Control* 2006;13:129-140.
9. Pommier RF, Vetto JT, Lee JT, Johnston KM. Synchronous non-small cell lung cancers. *Am J Surg* 1996;171:521-524.

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