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Case Reports

Atypical bronchial carcinoid tumours

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Introduction

Atypical carcinoids of the lung are rare neuroendocrine tumours, which are, according to their histologic characteristics, classified between typical carcinoid and small cell lung carcinoma. We describe three patients in whom, within 2 months, atypical carcinoid of the lung was diagnosed, and a fourth patient whose initial diagnosis of small cell lung carcinoma had to be revised after 5 yr. Probably the incidence of these tumours is underestimated, as their histologic differentiation from typical carcinoid and small cell carcinoma can be difficult.

Case Reports

CASE HISTORY 1

A 57-year-old woman was admitted in July 1992 because of dyspnoea and a productive cough. There was a 20-pack-yr history of cigarette smoking, until 1988. Physical examination only disclosed rhonchi at the right lung base, blood tests showed slight inflammation. Neurone specific enolase (NSE) and urinary 5-hydroxyindole-acetic acid were normal. On chest X-ray, atelectasis of the middle lobe was seen, CT scan revealed a tumour in the intermediate bronchus, with hilar lymphadenopathy and air trapping (Plate 1). Bronchoscopy showed a polypoid, fragile, endobronchial tumour, biopsy of which revealed atypical carcinoid (Plate 2). No metastases were detected. Echocardiography was normal. Right pneumonectomy was performed, disclosing invasion of mediastinal fat tissue, and absence of node involvement (pT3N0M0). Until now, there are no signs of metastasis or local progression of disease.

CASE HISTORY 2

In April 1992, on chest X-ray of a 48-year-old woman, a nodule was seen in the right lower lobe. The patient was an asymptomatic non-smoker and physical examination only showed crackles at the right lung base. Blood tests were normal, including NSE. CT scan confirmed the nodule in the right lower lobe, accompanied by enlarged mediastinal lymph nodes. Bronchoscopy was normal, and staging disclosed no distant metastases. Transthoracic needle aspiration biopsy showed small cell carcinoma. As treatment with carboplatin-etoposide for 2 months turned out to be unsuccessful, and as this might be a case of 'very limited' small cell lung carcinoma, resection was considered. Mediastinoscopy however proved ipsilateral lymph node involvement by atypical carcinoid, and restaging showed a scalp metastasis and a left parietal brain metastasis (proved by stereotactic biopsy) (cT2N2M1). Echocardiography was normal. The patient was treated with α-interferon, $3 \times 5{\cdot}10^{6}$E week^{-1}. After 2 months, for progressive paresis of the right leg, the brain metastasis was resected and pancranial radiotherapy was started. With interferon therapy, the metastases were stable but the lung nodule remained slowly progressive and became symptomatic, so in October 1993 a right lower lobectomy was performed. Immediate postoperative recovery was uneventful. One year later, the patient died of recurrent brain metastases.

CASE HISTORY 3

A 61-year-old man who smoked 40 cigarettes per day (60-pack-yr) presented in July 1992 with a chronic cough and weight loss. On physical examination breath sounds were diminished. Blood tests were

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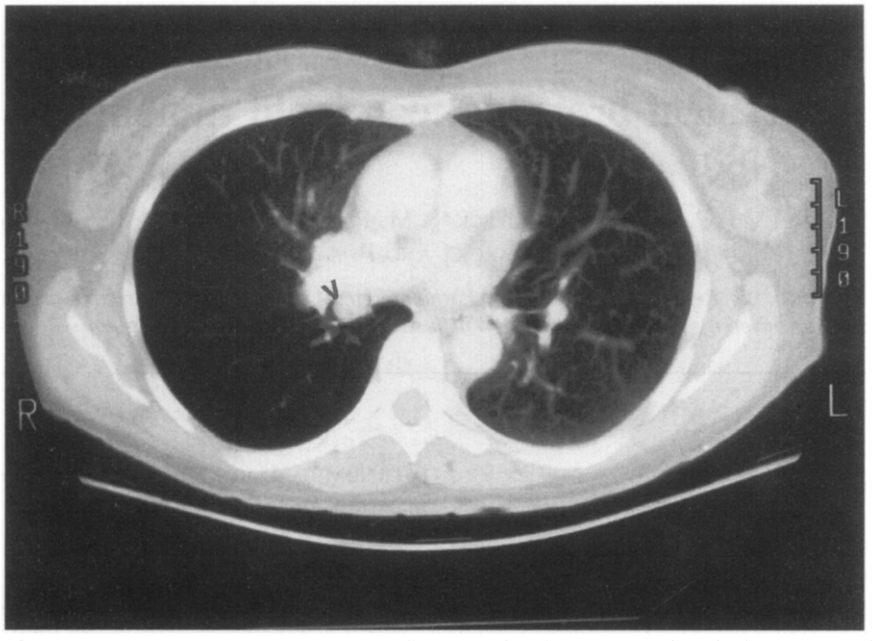

Plate 1 Chest CT scan, showing a tumour in the intermediate bronchus (arrow), hilar lymphadenopathy and air trapping (case 1).

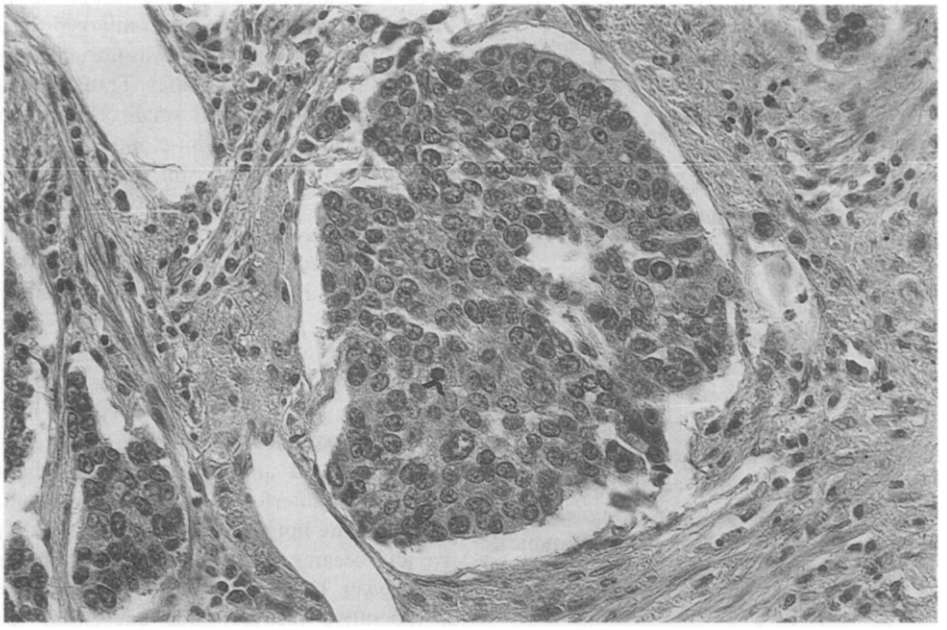

Plate 2 Small group of abnormal epithelial cells, with variable nuclear size and shape, and a mitosis (arrow): atypical carcinoid (case 1). (Hematoxylin and eosin, 350 ×).

normal, including NSE. Chest X-ray and CT scan showed a nodule in the right upper lobe, and emphysematous destruction of the lung parenchyma. On bronchoscopy the right upper lobe bronchus was occluded by a tumour, biopsy of which showed small cell carcinoma (Plate 3). As there were no distant metastases (cT1N0M0), lobectomy was performed; histologic examination of the resected tissue revealed

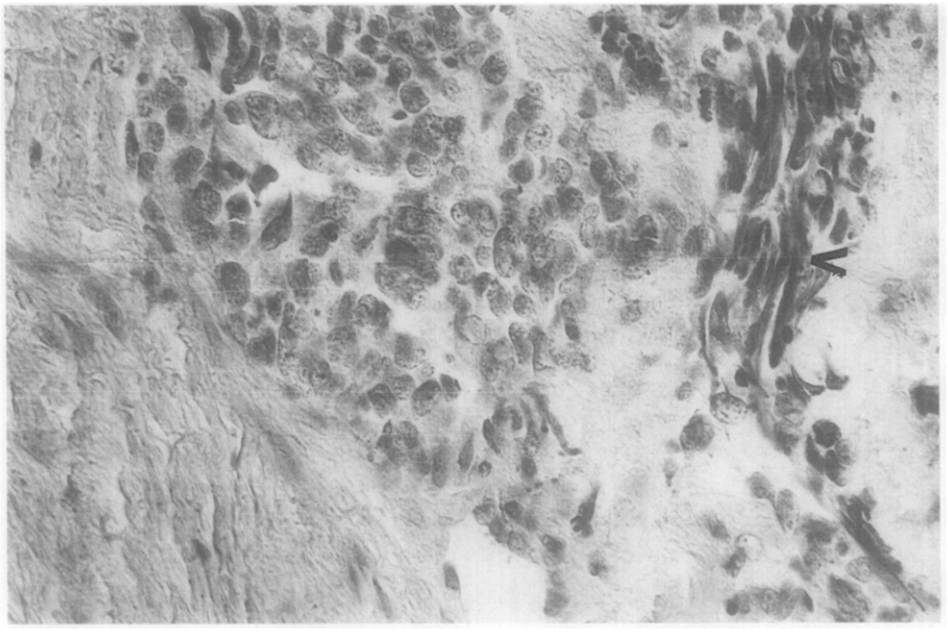

Plate 3 Biopsy of a nodule, on which small-cell carcinoma was diagnosed: a group of abnormal cells with enlarged, hyperchromatic nuclei with polymorphism. The cytoplasm is very scanty. On one side crush artefacts can be seen (arrow) (case 3). On examination of the resected nodule, it turned out to be an atypical carcinoid. (Hematozylin and eosin, 670 ×).

atypical carcinoid. A few weeks postoperatively, gait disturbances, a right Horner syndrome and left trigeminal neuralgia appeared. CT scan confirmed the presence of multiple brain metastases. Pancranial radiotherapy was started, followed by oral etoposide. The patient died 13 months after the initial diagnosis, of progressive cerebral metastases.

CASE HISTORY 4

In 1988, chest X-ray and CT scan of a 56-yr-old man showed a solitary nodule in the left upper lobe. There was a 35-pack-yr history of cigarette smoking, and for about 2 yr he had chest pain, increasing exertional dyspnoea and unproductive cough. Physical examination only showed an irregular pulse (which proved to be due to an atrial fibrillation on ECG), and blood tests, including NSE, were normal except for slightly increased alkaline phosphatase (bone fraction). Bronchoscopy showed no tumour, and there were no metastases. Lobectomy was performed, and histologically small cell carcinoma was diagnosed (pT2N0M0). Three cycles of adjuvant chemotherapy were administered (cyclophosphamide, doxorubicine, etoposide). The patient remains disease-free until now. This long survival raised doubts about the initial diagnosis, and indeed, after revision of the histologic sections, the diagnosis was changed into atypical carcinoid (Plate 4).

Discussion

Neuroendocrine tumours arise from mucosal APUD (amine precursor uptake and decarboxylation) cells. They contain neurosecretory granules, and are subdivided in typical carcinoid, atypical carcinoid (or well-differentiated neuroendocrine carcinoma) and small-cell neuroendocrine carcinoma (1,2). Some authors distinguish a fourth group: the large-cell neuroendocrine carcinoma (3). Neuroendocrine tumours represent a spectrum of malignancy and response to chemotherapy, increasing from carcinoid to small-cell carcinoma. Ultrastructurally, the number and size of the neurosecretory granules in small-cell carcinoma are smaller, as compared to carcinoid (1,4). Light microscopically, atypical carcinoid is distinguished from typical carcinoid by more numerous mitoses, cellular and nuclear polymorphism, hyperchromasia, a higher nucleus/cytoplasm ratio, more prominent nucleoli and the presence of necrosis (5). These characteristics are even more prominent in small-cell carcinoma (1,4,6). Immunocytochemical assay allows the demonstration of NSE, CEA, chromogranine A, synaptophysine, ACTH and other amines and peptides in the granules (1,6–8). As even the best marker, chromogranine A, is almost invariably present in carcinoid, but also in 20–50% of small-cell carcinomas, immunocytochemical assay is

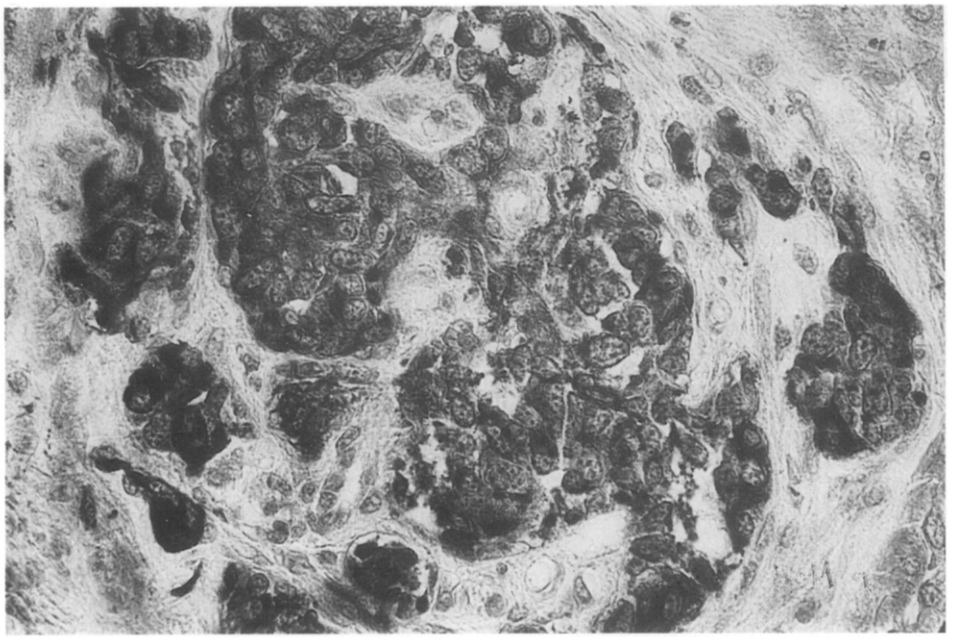

Plate 4 Immunoreactivity for chromogranine A in neoplastic cells from an atypical carcinoid (PAP-method) (case 4). (nuclear stain: hematoxylin, 670 ×).

not very useful for differentiation within the neuroendocrine tumour group (3,7). However, it is notable that the malignancy in these tumours is mainly a clinical feature, that does not completely correlate with the histologic aspect (9,10).

Differential diagnosis within the group of neuroendocrine tumours is often difficult, especially on endoscopically obtained biopsies; more than half of the atypical carcinoids is diagnosed then as typical carcinoid or small-cell carcinoma (2,11–13). Similarly, in two of our patients, the initial diagnosis on biopsy was small-cell carcinoma. In the literature (13,14), more than 25% of resected 'stage I small-cell carcinomas', turned out to be atypical carcinoids. This illustrates the importance of resection of 'stage I small-cell carcinomas', as this therapy may be curative if the tumour turns out to be atypical carcinoid.

Bronchial carcinoid represents 1–6% of all lung tumours, and 12% of all carcinoid tumours; only 7·5–11·5% of bronchial carcinoids are atypical (4,9). The mean age of diagnosis of patients with typical carcinoid is 35–50, and with atypical carcinoid 55–60, but the range is wide (13–80 years) (2,5,10,14–16). The male/female ratio mentioned in literature differs widely (2/1 to 0·6/1) (2,5,8,10,12,15,17–19). Typical carcinoid may be associated with the multiple endocrine neoplasia (MEN) syndrome, but not with smoking habits or asbestos exposure (1,11,4). In contrast, 50% of atypical carcinoid patients and even more than 95% of small-cell carcinoma patients are smokers. When 'small-cell carcinoma' is presumably diagnosed in a non-smoker under the age of 45, a carcinoid tumour should actively be excluded (4,11,12,15). This is illustrated by our second case.

Clinical manifestations depend on the site and the histologic type of the tumour: 80% of typical carcinoids are centrally located and cause slowly progressive bronchial obstruction with cough, fever, chest pain and local wheezing. Haemoptysis occurs in half of the cases, caused by the vascular nature of the tumour; atypical carcinoids rarely cause haemoptysis (4,9,10,11,18,20). Atypical carcinoids, which are often located peripherally, are frequently asymptomatic. Symptoms can also result from metastases, for typical bronchial carcinoids metastasize in 2–20% of cases, mostly to liver and bone, sometimes to the heart, breast or eyes. Atypical carcinoids metastasize in 60–70% of patients, and in addition to liver and bone, also to the brain: they already express the neurotropism of small-cell carcinoma (2–5,12). In our patients, the only symptoms were cough and chest pain; three of the four tumours were located peripherally, and in both patients who developed metastases, these were in the brain.

Carcinoid syndrome is seen in up to 13% of typical and atypical bronchial carcinoids, and in contrast with gastrointestinal carcinoid, the syndrome can be expressed without the presence of metastases.

None of our four patients expressed a carcinoid syndrome.

There are no specific serologic tumour markers for carcinoid; NSE can be slightly elevated; in our patients it was normal

On chest X-ray, centrally located tumours most often only show a retro-obstructive infiltrate or atelectasis. Peripheral tumours feature as a solitary nodule, sometimes lobulated, with a mean diameter of 4 cm, rare calcifications, and mostly located in the right upper lobe, the middle lobe or the lingula (2). The tumours are two to three times more frequent on the right side compared to the left side (10,18).

Bronchoscopy shows, in centrally located tumours, a friable polypoid or a submucosal infiltrating lesion (11).

Therapy of typical and localized atypical carcinoid is primarily surgical: conservative resection in sufficient in typical carcinoid; local recurrences nearly never develop. However, as in atypical carcinoid lymphatic involvement is frequent, a more radical resection, with lymph node dissection, is proposed (21). Postoperatively or in inoperable patients, an expectant attitude can be assumed if the patient is asymptomatic or if signs of aggressive tumour behaviour are lacking (9,11). Sometimes, preoperative partial tumour resection with a Nd-YAG laser is feasible, resulting in lung tissue sparing surgery.

Carcinoid tumours are much less sensitive to chemotherapy than small-cell carcinomas. 5-Fluorouracil, streptozotocin, doxorubicine, cyclophosphamide, dacarbazine and methotrexate have all been tested alone or in combination therapy, with a response rate of maximally 30–40%, and considerable side effects. Rarely, good clinical response to treatment with small-cell lung carcinoma protocols (doxorubicin, cyclophosphamide, etoposide and cisplatin, in different combinations) is reported (22,23). Alpha-interferon has a response rate of 47%, and its complications are less severe (9).

Radiotherapy can be used for brain metastases and symptomatic therapy of skin, liver and bone metastases (9).

Typical carcinoid has a favourable prognosis: a global median 5-yr survival of 87%: 96% in stage I, 71% in stages II and III, 11% in stage IV. Five-year survival of atypical carcinoid is 40–70%; that is why some authors suggest a more aggressive therapy (4,6,9,20,24). Prognosis is determined by histologic type, stage, operability and presence of symptoms (20,24). Considering the unfavourable prognosis of small-cell carcinoma, survival of more than 5 yr warrants revision of its diagnosis (4,14).

In conclusion, we would like to stress the importance of an exact histologic diagnosis of neuroendocrine bronchial carcinomas, as it considerably affects treatment and prognosis. Our patient series illustrates the therapeutic options and the diagnostic pitfalls.

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