Bolesław Papla[1], Marcin Zieliński[2], Jarosław Kuzdżał[2], Maria Harazda[2]

Hyperplasia of Endocrine Cells, Tumorlets and Atypical Carcinoid of the Lung – a Case Report

[1]Chair and Department of Clinical and Experimental Pathomorphology, Collegium Medicum, Jagiellonian University, Kraków,
[2]Pulmonary Hospital, Zakopane

The authors present an extremely rare case of endocrine cell hyperplasia, numerous tumorlets and atypical carcinoid situated in the left inferior pulmonary lobe of a 34-year old woman.

Introduction

In their classification of pulmonary and pleural tumors, Travis et al. [9] regard endocrine cell hyperplasia in the lung as a separate entity (diffuse idiopathic pulmonary neuroendocrine cell hyperplasia – DIPNECH). These diseases are, however, very rare and they differ from disseminated small tumors composed of neuroendocrine cells – the so-called tumorlets – that usually accompany chronic disease processes associated with bronchial obstruction [7, 8]. Also carcinoids and endocrine carcinomas constitute a separate group of neoplastic diseases. The issue of their interrelation remains an open question. The development of neuroendocrine cell hyperplasia in the lung, concomitant with numerous tumorlets and an atypical carcinoid with metastases into the lymph nodes is an unusual combination of processes associated with the pulmonary neuroendocrine system; such a combination of lesions is described in the present report.

A Case Description

A 34-year old female clerk, clinically asymptomatic, had had a chest X-ray performed when planning to start employment in another company. The X-ray demonstrated a tumor, 2cm in diameter, situated in the left inferior pulmonary lobe. Computed tomography revealed a tumor, 2.5×2cm in size, situated in the posterior basal segment (SX) of the left lung; the mass was characterized by varied density (30–50u.H) and was not enhanced following contrast administration (Fig. 1). Spirometry and bronchoscopy, as well as sputum cytology failed to disclose any abnormalities. In April 2003, at the thoracic surgery ward in Zakopane, the patient was subjected to a peripheral segmentectomy (the lateral and posterior basal segments – SIX and SX); the resected fragment of the lobe included a blue-reddish lesion that was macroscopically defined as an arteriovenous anastomosis and the procedure was completed. The intraoperative material was embedded in paraffin blocks, the remaining tissue was fixed in formalin and both were subsequently referred for consultation to the Chair of Pathomorphology, Collegium Medicum, Jagiellonian University, Cracow (No. 1513318). In addition to routine tests, the material was used in immunohistochemical reactions for chromogranin, synaptophysin, bombesin, ACTH and calcitonin.

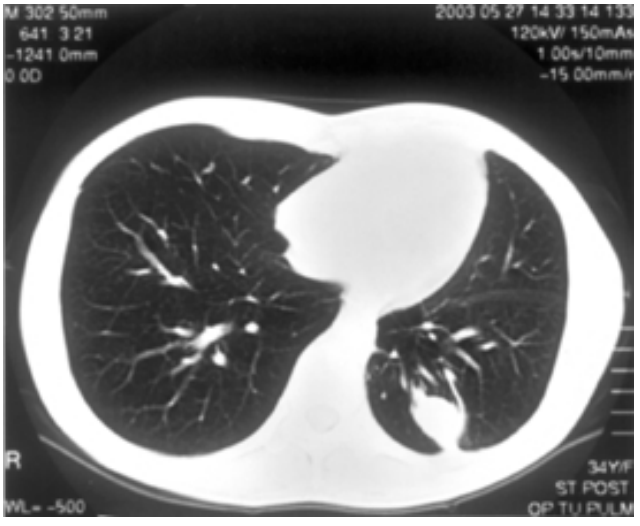

Fig. 1. A chest CT scan of the tumor situated in the left lung.

Histology revealed fairly numerous neuroendocrine cell tumorlets that were present in the walls and lumen of the small bronchi, at times completely filling the bronchioles (Figs. 2 and 3), in addition to small, pedunculated and attached to the walls papillary foci of neuroendocrine cell hyperplasia scattered peripherally in the alveoli, alveolar ducts and respiratory bronchioles (Figs. 4 and 5). These papillary hyperplastic le-

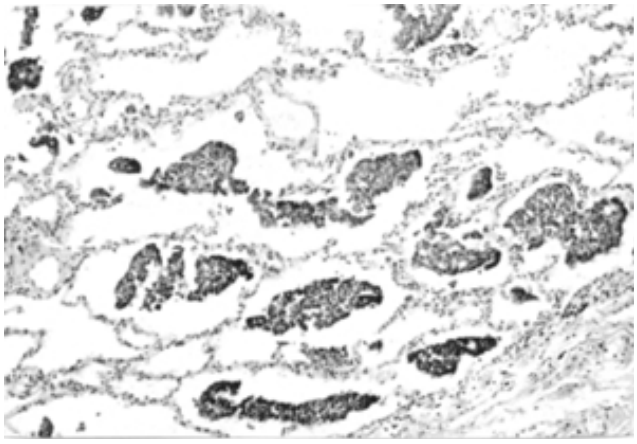

Fig. 2. Tumor-like growths of hyperplastic neuroendocrine cells filling the lumen of major bronchi and bronchioles. HE.

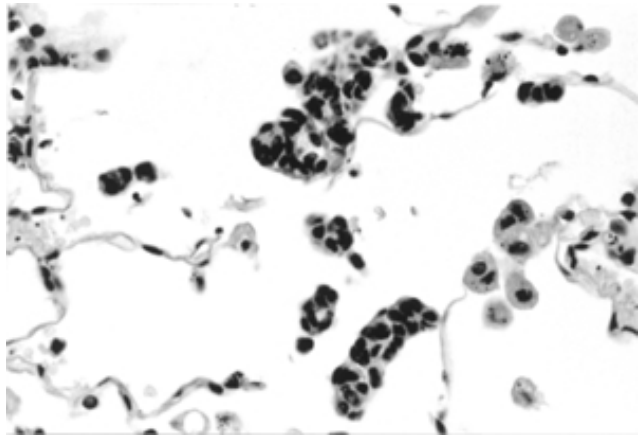

Fig. 5. Papillary-like structures with sparse stroma attached to the wall; note also isolated clusters of several neuroendocrine cells situated on the walls of the air structures – high magnification. HE.

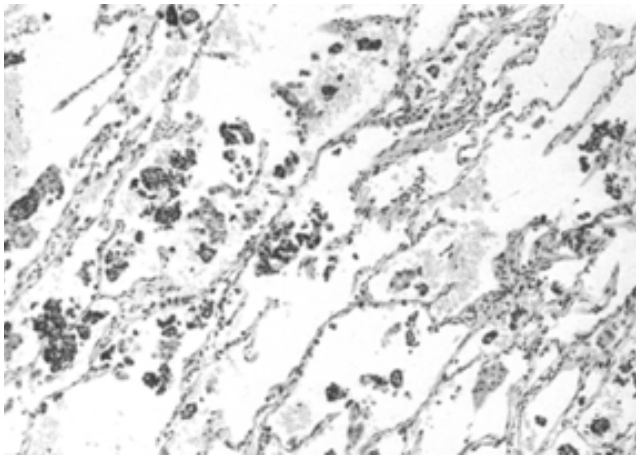

Fig. 3. Small, apparently loosely positioned, papillary-like structures composed mainly of neuroendocrine cells situated in lung segments peripheral in relation to the carcinoid. HE.

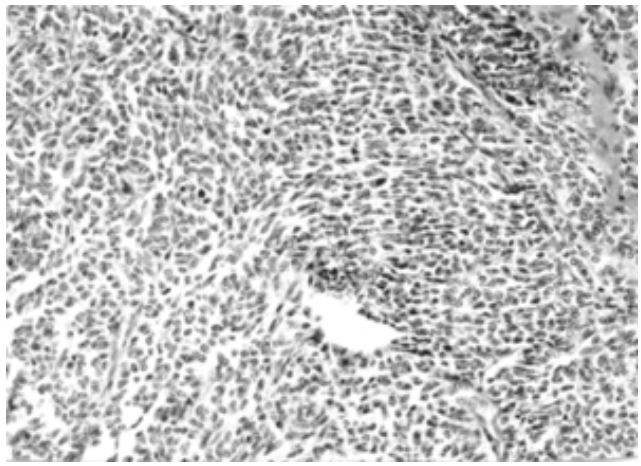

Fig. 6. A solid structure of the carcinoid, with mitotic figures seen in the central part. HE.

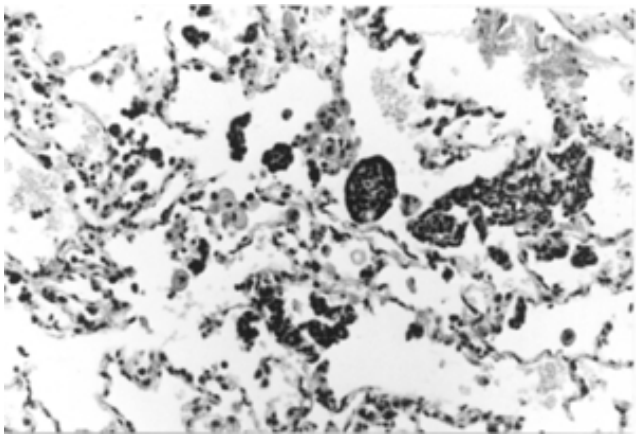

Fig. 4. Larger papillary-like structures and small neuroendocrine cell clusters in the terminal and respiratory bronchiolar lumen. HE.

sions were less numerous in the peripheral lung segments, but at times they penetrated as far as the pleura. Since the lesions, mostly in the form of tumorlets, extended to the margin of the resected tissue, and the repeated chest X-ray confirmed the presence of a lung tumor, in June 2003, the procedure was repeated, with the resection involving the entire inferior pulmonary lobe complete with the tumor, as well as the hilar and mediastinal lymph nodes. Histology (No. 1515642) revealed a tumor, 2cm in diameter, whose structure was predominantly that of atypical solid carcinoid, with a microscopically confirmed presence of up to three mitotic figures per 10 hpf (Fig. 6). Centrally within the tumor, a necrotic region was seen, most likely associated with the earlier surgical procedure. In 1/10 hilar nodes and 3/7 mediastinal nodes carcinoid metastases were noted. Postoperatively, the patient has been doing fairly well, demonstrating transient signs of brachial plexus paresis. She was placed on chemotherapy and by January 2004, she had received 6 cycles (carboplatin + wepeside); at present, she is followed up by an oncologist. The patient has no symptoms of the disease; imaging methods (X-ray and CT) do not confirm any relapses.

In immunohistochemistry, carcinoid cells were positive for chromogranin and synaptophysin, the majority was positive for bombesin (gastric releasing factor), and less numerous cells showed a positive reaction to ACTH and calcitonin. The hyperplastic cells within the pulmonary alveoli and bronchioles showed similar reactions.

Discussion

The neuroendocrine Kulchitsky cells are abundant in the neonatal period, both within the walls of large bronchi, where they form small clusters, and in small bronchi as isolated cells scattered among epithelial cells. Their role is most likely associated with the initiation of the respiratory function in the postnatal period. Hyperplasia of these cells has been noted in individuals inhabiting high altitude dwellings or in mountain climbers and this phenomenon is believed to result from adaptation to oxygen deficiency [1]. The substances produced by these cells exert a local autocrine and paracrine effect on epithelial cells, fibroblasts and muscle cells and may be associated with the pathogenesis of various processes occurring in the lungs. In the described case, the situation was different and we found no processes within the stroma of the lung that normally occur concomitantly with tumorlets or neuroendocrine cell hyperplasia. This finding supports the hypothesis proposed by Aguayo et al. [1] that neuroendocrine cell hyperplasia may precede other processes in the lungs, mainly of inflammatory-fibrous character, as an effect of their paracrine secretion. Similar conclusions were also reached by Armas et al. [2].

Tumorlets, described for the first time by Whitwell in 1955, constitute small clusters of neuroendocrine cells situated in the walls of major bronchi, usually associated with their partial obstruction and fibrosis developing in the vicinity; such clusters are incidentally found in resected samples of pulmonary tissue. They are termed "microcarcinoids", but their association with bronchial carcinoids, both situated centrally or peripherally, is unclear. Tumorlets as a rule are small, below 1cm in diameter (3–5mm) and multiple. In isolated cases, they may metastasize to regional lymph nodes [5]. According to [6, 9], up to 76% of peripheral pulmonary tissue samples analyzed following the resection of peripheral carcinoids demonstrate neuroendocrine cell hyperplasia, but to-date it has not been determined whether this phenomenon represents a reaction to the presence of a tumor or whether it should be regarded as a preneoplastic state.

While pondering on the etiology of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), Cohen et al. [4] demonstrated a high expression rate of neutral endopeptidase, what was contrary to the preliminary thesis proposed by these authors, stating that the hyperplasia may result from low endopeptidase activity and a failure of bombesin and other peptides to break down, leading in consequence to their intensified autocrine and paracrine activity. In neuroendocrine cancers of the lungs, a low level of this neutral endopeptidase was previously observed [3].

In the presented case, neuroendocrine cell hyperplasia resulting in the formation of papillary-like structures, might to a degree be associated with bronchial obstruction due to the carcinoid increasing in size and narrowing the bronchial lumen. Yet, a congenital malformation of the pulmonary neuroendocrine system is more likely in this patient. The hypothesis presented by Armas et al. [2] of a dissemination of atypical carcinoid, similarly to the process occurring in the case of bronchioalveolar carcinoma, is less likely. All the presented lesions occurring together constitute a rare and exceptional case, what has been confirmed by numerous European specialists in lung pathology who have been asked to evaluate the case (Ph. Hasleton, H. Popper, F. Galateau-Salle and others).

In view of the carcinoid metastasizing into the lymph nodes, despite the chemotherapy, the prognosis in our patient is rather poor, but the follow-up after the procedure is too short to allow for any firm conclusions.

References

1. *Aguayo SM, Miller YE, Waldron JA et al:* Brief report: Idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells and airways disease. New Engl J Med 1992, 327, 1285–1292.
2. *Armas OA, White DA, Erlandson RA, Rosai J:* Diffuse idiopathic pulmonary neuroendocrine cell proliferation presenting as interstitial lung disease. Am J Surg Pathol 1995, 19, 963–970.
3. *Cohen AJ, Bunn WF, Franklin C et al:* Neutral endopeptidase variable expression in human lung, inactivation in lung cancer, and modulation of peptide induced calcium flux. Cancer Res 1996, 56, 831–839.
4. *Cohen AJ, King TE, Gilman LB et al:* High expression of neutral endopeptidases in idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells. Am J Resp Crit Care Med 1998, 158, 1593–1599.
5. *D'Agati VD, Perzin KH:* Carcinoid tumorlets of the lung with metastasis to peribronchial lymph node. Report of a case and review of the literature. Cancer 1985, 55, 2472–2476.
6. *Miller R, Muller NL:* Neuroendocrine cell hyperplasia and obliterative bronchiolitis in patients with peripheral carcinoid tumors. Am J Surg Pathol 1995, 19, 653–658.
7. *Papla B:* Badania immunohistochemiczne guzeczków płucnych (tumorlets). XIII Zjazd Naukowy PTP Rzeszów 1995. Pol J Pathol 1995, 46, 128(abs).
8. *Pelosi G, Zancanaro C, Sbabo L et al:* Development of innumerable tumorlets in pulmonary lobe scarred by intralobular sequestration. Immunohistochemical and ultrastructural study of an unusual case. Arch Pathol Lab Med 1992, 116, 1167–1174.
9. *Travis WD, Colby TV, Corrin B et al:* Histological Typing of Lung and Pleural Tumours. WHO International Histological Classification of Tumours. 3rd ed. Springer, Berlin 1999, 30.

Address for correspondence and reprint requests to:
B. Papla M.D.
Department of Pathomorphology,
Collegium Medicum, Jagiellonian University,
Grzegórzecka 16, 31-531 Kraków