

Brief Report

CUSHING'S SYNDROME CAUSED BY
CORTICOTROPIN SECRETION
BY PULMONARY TUMORLETS

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THE term "pulmonary tumorlets" describes multiple microscopic nests of neuroendocrine cells in the lungs.¹ Like bronchial carcinoid tumors and small-cell carcinomas, pulmonary tumorlets arise from Kulchitsky's cells. In the lung the abnormalities in these cells range from hyperplasia to malignant transformation, since control over cellular growth is lost.²

Both bronchial carcinoid tumors and small-cell lung carcinomas may secrete corticotropin in sufficient quantities to cause Cushing's syndrome. We describe a patient with Cushing's syndrome due to ectopic secretion of corticotropin in whom the source of the excess corticotropin was ultimately found to be hundreds of tumorlets in one lobe of the lungs.

CASE REPORT

A nine-year-old girl presented to the National Institutes of Health Clinical Center with weight gain, growth arrest, hypertension, abdominal striae, acne, hirsutism, proximal muscle weakness, mood swings, and increasing skin pigmentation. There was no family history of endocrine disease. Her 24-hour urinary cortisol excretion was 470 μg (1300 nmol), as compared with a normal 24-hour excretion of 20 to 90 μg (55 to 250 nmol). The plasma corticotropin concentration was 200 pg per milliliter (44 pmol per liter), as compared with a normal concentration of 5 to 26 pg per milliliter (1 to 6 pmol per liter). The plasma cortisol concentration was 28 μg per deciliter (770 nmol per liter), as compared with a normal concentration of 7 to 25 μg per deciliter (190 to 690 nmol per liter). The urinary cortisol excretion did

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not decline in response to the administration of dexamethasone (2 mg every six hours for two days). The results of magnetic resonance imaging (MRI) of the pituitary were normal. Sampling of the inferior petrosal sinuses did not reveal a gradient in plasma corticotropin concentrations between the petrosal sinuses and the peripheral vein. These findings suggested that the patient's Cushing's syndrome was caused by ectopic secretion of corticotropin. Imaging studies of the neck, chest, abdomen, and pelvis were normal. Sampling of the thymic vein revealed a 2:1 gradient in the plasma corticotropin concentration between the thymic vein and a peripheral vein. Thymic arteriography revealed a 0.5-by-0.5-cm mass within the thymus. The patient underwent thymectomy, which did not lower her plasma corticotropin concentration. The mass within the thymus proved to be an ectopic parathyroid gland; the thymus was otherwise normal.

The patient was treated with ketoconazole alone and then in combination with the glucocorticoid antagonist mifepristone, but the drugs did not control the hypercortisolism. One year later, because of complete arrest of growth, she underwent bilateral adrenalectomy, after which she was treated with replacement doses of hydrocortisone and fludrocortisone. The clinical manifestations of Cushing's syndrome disappeared, and her growth rate increased. After surgery, she was followed with annual examinations; computed tomography (CT) or MRI of the neck, chest, abdomen, and pelvis; total-body pentetreotide scanning; and measurements of plasma corticotropin. She remained asymptomatic, grew at a normal rate, and had a normal menarche at the age of 11 years. Physical examination found only mild, stable hyperpigmentation. The plasma corticotropin concentration measured 14 to 16 hours after the administration of hydrocortisone ranged from 300 to 400 pg per milliliter (66 to 88 pmol per liter). All the scans were normal.

At 19 years of age, she presented with increased pigmentation of her knuckles and gums; her physical examination was otherwise normal. Plasma corticotropin concentrations ranged from 800 to 900 pg per milliliter (176 to 198 pmol per liter), and the plasma corticotropin-releasing hormone concentration was 22 pg per milliliter (4.6 pmol per liter), as compared with a normal concentration of 24 to 40 pg per milliliter (5.0 to 8.4 pmol per liter). CT of the chest revealed multiple small (1 to 8 mm) nodules confined to the right lower lobe (Fig. 1). The nodules were consid-

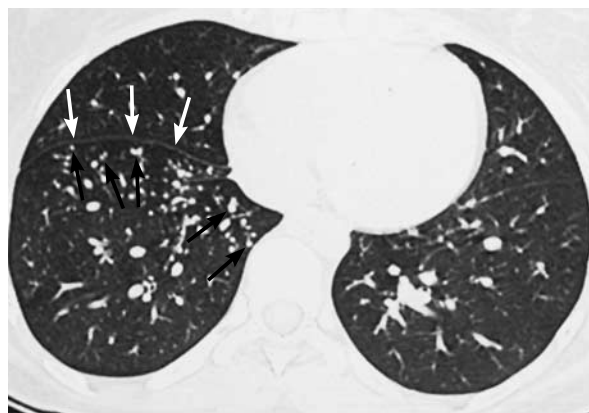
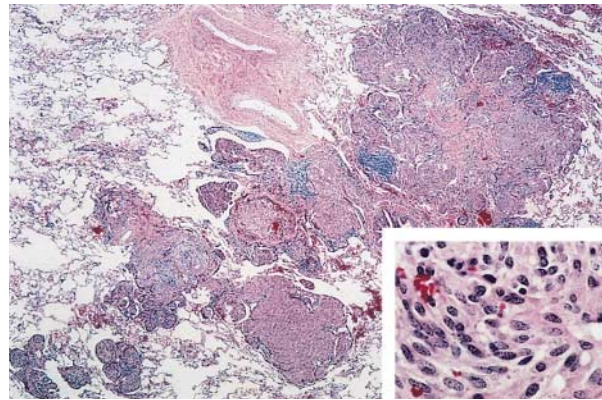
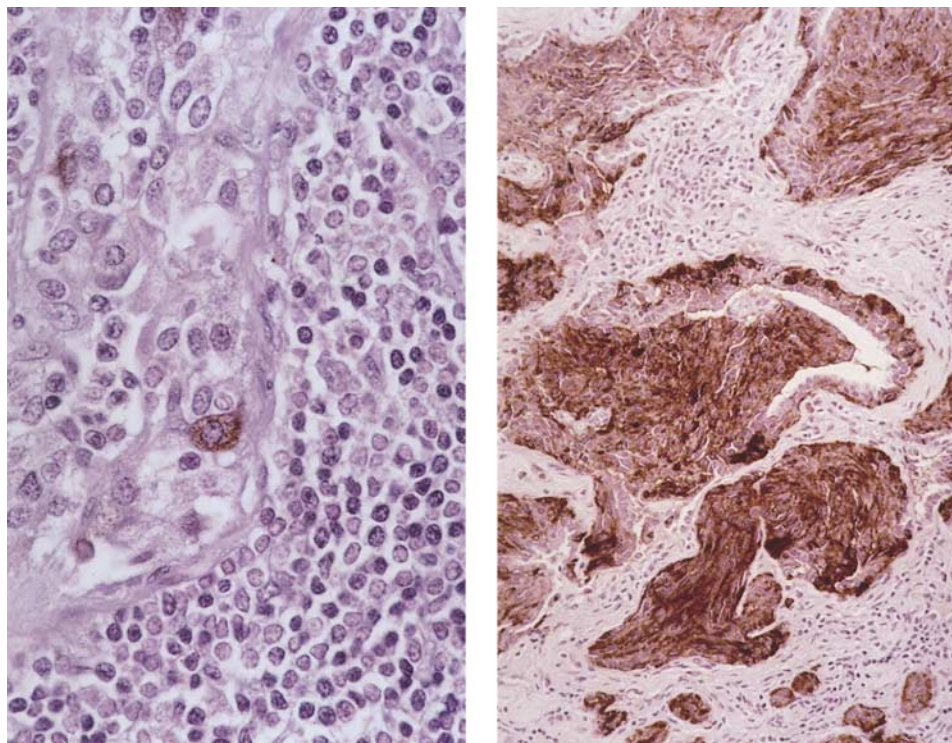


Figure 1. High-Resolution Computed Tomography of the Lungs of a 19-Year-Old Woman with Excess Corticotropin Secretion.

There are multiple 1-to-8-mm nodules (black arrows) in the right lower lobe, particularly the anterior portion immediately behind the major fissure (white arrows). The right middle lobe and left lung contain no nodules. Other CT sections confirmed that the nodules were largely confined to the subpleural areas of the right lower lobe. There was no hilar or mediastinal adenopathy.



A



B

Figure 2. Microscopical Sections of Pulmonary Tumorlets.

In Panel A, pulmonary tumorlets are seen as a cluster of nodules organized around a bronchiole (hematoxylin and eosin, $\times 25$). The inset shows the typical neuroendocrine appearance of the tumorlet cells (hematoxylin and eosin, $\times 200$). In Panel B, immunoperoxidase staining with anticorticotropin antibody shows corticotropin in scattered tumorlet cells (left-hand panel, $\times 600$), whereas staining with antichromogranin antibody reveals intense staining in many tumorlet cells (right-hand panel, $\times 200$).

ered inaccessible to percutaneous or transbronchoscopic biopsy. The results of pulmonary-function tests were normal. Tests for laboratory markers of infectious or granulomatous diseases were negative. The pentetreotide scan was negative. Selective pulmonary venous sampling revealed no higher corticotropin concentration than in peripheral-vein plasma, but the vein draining the right lower lobe could not be cannulated. Nevertheless, the gradient from the thymic vein to the peripheral vein that had been found earlier (which can be increased in patients with lung

lesions³) led us to conclude that the lesions seen on CT were responsible for the ectopic secretion of corticotropin.

The patient underwent a right lower lobectomy. The lobe contained hundreds of lesions less than 1 cm in diameter, whereas the right middle and upper lobes appeared normal. The left side of the chest was not explored. Plasma corticotropin concentrations were undetectable soon after surgery. Three months after surgery, there was improvement in the patient's pigmentation; plasma corticotropin concentrations were 160 to 180 pg per milliliter (35 to

40 pmol per liter) 14 hours after the last dose of hydrocortisone, values consistent with adrenalectomy. CT of the chest revealed no abnormalities beyond the right lower lobectomy.

The parenchyma of the lung contained approximately 1500 discrete, white, firm nodules measuring 1 to 8 mm in diameter; a precise count of the nodules by detailed serial sections was not obtained. The intervening parenchyma was normal. Microscopic examination of the nodules (Fig. 2A) revealed nests of spindle cells (tumorlets) with oval nuclei and speckled chromatin. Mitotic figures were not seen. The nests were located within and around bronchioles and varied in size from 100 μ m to 8 mm in diameter. Immunohistochemical staining of the nodules revealed scattered cells containing corticotropin (Fig. 2B) and many cells containing chromogranin A, synaptophysin, and cytokeratins AE1 and AE3, confirming their neuroendocrine origin.

DISCUSSION

This patient had severe corticotropin-dependent Cushing's syndrome, which was treated by bilateral adrenalectomy because the source of the excess corticotropin could not be identified. Tumorlets of the lower lobe of the right lung were identified as the source of excess corticotropin 10 years later, but it seems likely that they were present initially. The time from presentation to diagnosis is within the limits reported for bronchial carcinoid tumors that cause Cushing's syndrome.⁴ On retrospective examination of the patient's CT studies, small lesions were found to be present at least five years before lobectomy. Whether the tumorlets were confined to the right lower lobe remains unanswered, but there was no evidence of other tumorlets or excess corticotropin secretion six months after surgery. Why tumorlets should be confined to one lobe of the lung, if that is indeed the case, is not known.

Ectopic hormone production by pulmonary tumorlets is very rare. We are aware of only two other patients in whom ectopic secretion of corticotropin from pulmonary tumorlets may have caused or at least contributed to Cushing's syndrome. One was a 39-year-old man with an abscess in the right upper lobe in whom pulmonary tumorlets were found in lung tissue excised during a therapeutic lobectomy.⁵ Histologic examination showed well-differentiated neuroendocrine cells with low mitotic indexes. Cushing's syndrome developed three months after the operation, at which time the patient had diffuse bilateral lung disease. He died from widespread tumorlet micrometastases, suggesting that one or more tumorlets had undergone malignant transformation. The second patient was a 61-year-old woman with a history of smoking who presented with hemoptysis and Cushing's syndrome.⁶ She had a left-upper-lobe mass that proved to be a small-cell lung carcinoma that was surrounded by 14 to 16 benign-appearing nests of neuroendocrine cells of various sizes. Immunohistochemical studies revealed corticotropin in the neuroendocrine-cell nests, suggesting that the carcinoma originated from one of the tumorlets.

The concept of a diffuse neuroendocrine system consisting of epithelial cells with characteristic mor-

phologic and histochemical properties that have important paracrine regulatory functions antedates the description of pulmonary tumorlets.⁷ The recognition of this system gave rise to the theory that a "neuroepithelial chemoreceptor body" within the lung tissue facilitated the pattern of bronchial branching in early lung development and coordinated the repair processes during inflammation in postnatal life.^{8,9} Fetal lungs, as compared with adult lungs, have an abundance of neuroendocrine cells. Neuroendocrine-cell hyperplasia is frequently observed in adults living at high altitude, in cigarette smokers, and in patients with chronic lung disease.

Pulmonary tumorlets were initially considered to represent an extreme state of neuroendocrine-cell hyperplasia, usually associated with chronic inflammatory conditions such as cystic fibrosis² and bronchiectasis.¹⁰ They have also been reported as incidental findings in patients with no lung disease. The exact incidence of tumorlets is not known, but in one study they were found at autopsy in 2 of 1900 patients with no lung disease and in 22 of 2400 lung specimens surgically removed for various causes.¹

Pulmonary tumorlets and bronchial carcinoid tumors are believed to originate from the same cells, but they are considered separate entities because of several distinguishing features. Bronchial carcinoids are usually solitary masses, larger than 0.5 cm and located centrally, whereas pulmonary tumorlets are small, peripheral, and multiple. The pathological features that distinguish tumorlets from bronchial carcinoids are the lack of a capsule (except for a fibro-lamellar membrane encircling the nests) and the lack of a vascular supply (except for primitive lymphatic ducts) in tumorlets. The malignant potential of tumorlets has been apparent since their resemblance to bronchial carcinoids was noted. However, metastases to bronchopulmonary, hilar, and mediastinal lymph nodes or more distant sites have been reported in only a few patients.

In conclusion, pulmonary tumorlets should be considered in the differential diagnosis of Cushing's syndrome due to ectopic corticotropin secretion. For a patient with no apparent nonendocrine tumor, who must therefore be treated by bilateral adrenalectomy, periodic CT or MRI is indicated to detect small, slow-growing lesions such as pulmonary tumorlets.

REFERENCES

1. Whitwell E. Tumorlets of the lung. *J Pathol Bacteriol* 1955;70:529-41.
2. Bonikos DS, Archibald R, Bensch KG. On the origin of the so-called tumorlets of the lung. *Hum Pathol* 1976;7:461-9.
3. Doppman JL, Pass HI, Nieman LK, et al. Corticotropin-secreting carcinoid tumors of the thymus: diagnostic unreliability of thymic venous sampling. *Radiology* 1992;184:71-4.
4. Pass HI, Doppman JL, Nieman L, et al. Management of the ectopic ACTH syndrome due to thoracic carcinoids. *Ann Thorac Surg* 1990;50:52-7.
5. Rodgers-Sullivan RF, Weiland LH, Palumbo PJ, Hepper NG. Pulmonary tumorlets associated with Cushing's syndrome. *Am Rev Respir Dis* 1978; 117:799-806.

6. Ranchod M. The histogenesis and development of pulmonary tumorlets. *Cancer* 1977;39:1135-45.
7. Pagel W. Über den Zusammenhang von ungewöhnlichen Wucherungen atypischen und ortsfremden Epithels der Bronchien mit Bronchiektasien: Untersuchungen über adenomartige Verästelungen der Bronchien des Meerschweinchens. *Virchows Arch Pathol Anat* 1927;263:583-94.
8. Gould VE, Linnoila RI, Memoli VA, Warren WH. Neuroendocrine

components of the bronchopulmonary tract: hyperplasias, dysplasias, and neoplasms. *Lab Invest* 1983;49:519-37.

9. Tateishi R. Distribution of argyrophil cells in adult human lungs. *Arch Pathol* 1973;96:198-202.

10. Watanabe H, Kobayashi H, Honma K, Ohnishi Y, Iwafuchi M. Diffuse panbronchiolitis with multiple tumorlets: a quantitative study of the Kulchitsky cells and the clusters. *Acta Pathol Jpn* 1985;35:1221-31.



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