Bronchiolar carcinoma: a case report with pulmonary function studies

N. H. DYER¹, D. T. D. HUGHES, AND J. M. A. THOMPSON

From the London Hospital, London, E.1

A patient with bilateral multinodular bronchiolar carcinoma is described in whom carbon monoxide transfer factor and arterial oxygen saturation were greatly impaired but lung volumes and ventilation were only minimally reduced. We record this because we have not found previous reports of detailed pulmonary function studies in this condition.

A 57-year-old man was admitted to hospital in August 1965 with a three-week history of breathlessness and cough which was initially dry but one week later became productive of a moderate quantity of mucoid sputum. He also complained of shivering, sweating, palpitations, lassitude, insomnia, anorexia, and a weight loss of 8 lb. (3.6 kg.). He denied any other symptoms, including chest pain and haemoptysis. He had spent most of his working life in furniture factories but had not been exposed to any industrial risk and there were no previous respiratory symptoms. He smoked 20 cigarettes per day.

On examination he was an ill, wasted man weighing 115 lb. (52 kg.). He was afebrile on admission but subsequently showed occasional spikes of temperature to 99° F. (37.2° C.). Shotty lymph nodes were palpable in the right anterior triangle of the neck and in both inguinal regions. Clubbing of the nails was not present. There was obvious central cyanosis and the respiratory rate varied from 17 to 36 respirations per minute, with much activity of the accessory muscles of respiration. Chest movements were normal and equal but the trachea was deviated to the right, and the percussion note, vocal fremitus, and breath sounds were reduced at the right lung base. Fine and coarse crepitations were scattered throughout the lower parts of both lungs. The pulse rate was 95 per minute, regular, but the volume was diminished; the blood pressure was 150/70 mm. Hg. There was no evidence of heart failure. A forcible right ventricular heave was present. There was a systolic murmur at the tricuspid area. The liver was palpable three fingerbreadths below the right costal margin. Bilateral inguinal

herniae and a right-sided hydrocoele were present.

The haemoglobin was 18.3 g./100 ml. (125%) and the leucocyte count was 18,200 per c.mm., 85% of which were neutrophils. Blood urea, electrolytes, liver function tests, and E.S.R. (Westergren) were normal. An E.C.G. revealed right atrial hypertrophy and right axis deviation with low voltage in all limb leads. The chest radiograph showed numerous small opacities scattered throughout the middle and lower zones of both lung fields, with an area of consolidation and partial collapse involving the right lower lobe (Fig. 1). Tomograms indicated an opacity in the region of the right middle and lower lobe bronchus which had the appearance of an enlarged lymph node. Sputum culture produced coliform organisms on several occasions, and cytological examination revealed cells suggestive of adenocarcinoma, some of which contained large intracytoplasmic vacuoles filled with mucin, in three out of four specimens. Pulmonary function studies were performed by the methods in routine use at the London Hospital (Hughes and Lee, 1963) and the results are shown in the Table. These indicate a high minute volume, a low normal PACO_2 , slight uniform reduction of lung volumes, a normal R.V./T.L.C. ratio, minimal airways obstruction with an F.E.V._{1.0} which is 64% of the vital capacity, and severe reduction in transfer factor and arterial oxygen saturation.

He remained ill and breathless to an extent which made the performance of lung function studies difficult. There was temporary improvement on high doses of prednisone (60 mg. per day) followed by deterioration possibly associated with reduction of the dosage. Intravenous mustine was of no benefit and he died 10 weeks after the onset of his symptoms.

¹Present address: St. Bartholomew's Hospital, London, E.C.1

FIG. 1. Chest radiograph. Bilateral multinodular disease with diffuse shadowing on the right of the cardiac shadow.

TABLE
PULMONARY FUNCTION STUDIES

Ventilation			
Respiratory rate	17/min.		
Tidal volume	1,400 ml.		
Minute volume	24 l./min.		
Vital capacity (Bernstein spirometer)	3,250 ml.		
F.E.V. _{1.0} (Bernstein spirometer)	2,050 ml.		
% F.E.V. _{1.0} /V.C.	64%		
Blood Gases			
PACO ₂ (rebreathing)	36 mm.Hg		
Arterial O ₂ saturation	63.5%		
Lung Volumes (Godart Pulmotest)			
	Observed	Predicted	% Predicted
Vital capacity (ml.)	3,400	3,900	86
Inspiratory capacity (ml.)	2,500	2,600	86
Expiratory reserve volume (ml.)	1,250	1,300	96
Functional residual capacity (ml.)	3,100	3,700	83
Residual volume (ml.)	1,850	2,400	77
Total lung capacity (ml.)	5,250	6,300	83
% R.V./T.L.C.	35		
Transfer factor	6	23	26
Total blood volume (Volemetron)	5.9 l.	3.6 l.	164

PATHOLOGY

Necropsy was performed 34 hours after death. A careful search for a possible source of primary carcinoma was made, but none was found. No tumour was present outside the chest. There were bilateral, pale yellow, pleural effusions of about 500 ml. The heart was normal apart from pericardial adhesions and mild right ventricular hypertrophy (the wall measured 0.6 cm. in thickness). Both lungs were heavy, retained their shape when removed from the chest, and contained nodules of grey-white tumour, particularly in the left lower lobe. The right lower lobe was almost solid, showing a diffuse 'pneumonic' spread (Fig. 2) which formed a fern-leaf pattern on the pleural surface, resembling the spread of bronchopneumonia (no exact site of origin could be identified). There was involvement of superficial lymphatics by tumour which formed a fine beading most noticeable on the sharp edges of the lobe. The bronchi were apparently thickened by 'peri-

FIG. 2. Cut surface of the right lower lobe. Fixation by intrabronchial formalin inflation.

bronchial' spread of tumour. The hilar and subcarinal lymph nodes contained metastases.

MICROSCOPY

Tumour cells were regularly arranged in a single layer around the alveolar walls (Fig. 3). They were mostly columnar with an oval basal nucleus which contained a prominent nucleolus, but in some areas the cells were more rounded and occasionally the alveoli were lined by a thin layer of small cuboidal cells. Mitoses were absent. There was abundant mucin production, and an occasional group of ciliated cells could be found. Papillary projections were frequent (Fig. 4), with a variable amount of exfoliation. In some areas of the right lower lobe exfoliation was profuse and alveoli were completely filled with mucin and tumour cells, forming a 'tumour pneumonia'. In the more densely involved areas there was a definite stroma containing young collagen. Elsewhere the underlying lung was free from interstitial fibrosis. Tumour extended up to but not through the pleura. The subpleural, intrapulmonary, and bronchial submucosal lymphatics contained tumour. Many intrapulmonary lymphatics were dilated. Other vessels were free, and no obliteration by external compression (Liebow, 1956) was seen. In the other lobes tumour was more nodular although sometimes confluent, but the same

FIG. 3. Alveolar septa lined by tumour cells. H. and E., $\times 480$.

FIG. 4. Arrangement of tumour cells with papillary projection. Elastic Van Gieson, $\times 120$.

cellular arrangement and so-called lepidic spread, in which the cells used the alveoli as scaffolding and stroma, was always present. A similar 'alveolar arrangement' was seen in the lymph node metastases.

DISCUSSION

Cases of bronchiolar carcinoma are now being recognized with increasing frequency, and many reports have appeared in the literature, including the excellent reviews of Storey, Knudtson, and Lawrence (1953), Liebow (1960), and Watson and Farpour (1966).

There is a variable gross anatomical pattern, but three main groups may be recognized on radiography or at necropsy, *i.e.*, an isolated nodule, multiple bilateral nodules, and diffuse or 'pneumonic' involvement of a segment or lobe (Liebow, 1960). It therefore follows that the results of lung function studies will vary with the different types, and the degree of functional impairment will reflect the extent of the lung tissue replaced by carcinoma (Bates and Christie, 1964). Two cases are mentioned by these authors. In the first the carcinoma involved most of one lobe but pulmonary function was little disturbed. The second had bilateral involvement which was associated with reduction in lung volumes but preservation of

ventilatory function. Although bronchiolar carcinoma is listed among the causes of 'alveolar-capillary block' (Comroe, Forster, DuBois, Briscoe, and Carlsen, 1962) or widespread involvement of tissues distal to the terminal bronchiole (Cotes, 1965), no further details are given.

Our patient had developed bilateral multinodular disease with more diffuse involvement of the right lower lobe. There was some clinical and pathological evidence of pulmonary hypertension. The disturbance of lung function included slight reduction of lung volumes, hyperventilation at rest which was suggested by a high minute volume and low normal $PACO_2$, severe arterial oxygen desaturation at rest with secondary polycythaemia, and marked reduction in transfer factor. The very low transfer factor and desaturation at rest indicate that the functional disturbance must be more than a simple diffusion barrier and suggest ventilation-perfusion inequality (Campbell, 1965). Similarly, although carcinoma cells lining the alveoli and interstitial collagen deposition provide a good histological model for the discredited alveolar-capillary block syndrome, the anatomical picture with lymphatic permeation, 'tumour pneumonia', capillary bed involvement, etc., equally well results in ventilation-perfusion disturbance.

We should like to thank Dr. K. M. A. Perry for permission to publish details of this case and for his help and advice; Mr. R. Hammond and Mr. R. Ruddick for the photographs; and Mrs. M. Burnard for technical and secretarial help.

REFERENCES

- Bates, D. V., and Christie, R. V. (1964). *Respiratory Function in Disease*, p. 411. W. B. Saunders, Philadelphia.
- Campbell, E. J. M. (1965). Respiratory failure. *Brit. med. J.*, 1, 1451.
- Comroe, J. H., Forster, R. E., DuBois, A. B., Briscoe, W. A., and Carlsen, E. (1962). *The Lung*, 2nd ed., p. 111. Year Book Medical Publishers, Chicago.
- Cotes, J. E. (1965). *Lung Function*, p. 337. Blackwell Scientific Publications, Oxford.
- Hughes, D. T. D., and Lee, F. I. (1963). Lung function in patients with systemic sclerosis. *Thorax*, 18, 16.
- Liebow, A. A. (1956). *Pulmonary Carcinoma*, ed. E. Mayer and H. C. Maier, p. 156. New York University Press.
- (1960). Bronchiolo-alveolar carcinoma. *Advanc. intern. Med.*, 10, 329. Year Book Publishers, Chicago.
- Storey, C. F., Knudtson, K. P., and Lawrence, B. J. (1953). Bronchiolar ('alveolar cell') carcinoma of the lung. *J. thorac. Surg.*, 26, 331.
- Watson, W. L., and Farpour, A. (1966). Terminal bronchiolar or 'alveolar cell' cancer of the lung'. Two hundred and sixty-five cases. *Cancer*, 19, 776.