LYMPHANGITIS CARCINOMATOSA

BY

G. N. CHANDLER, B.M., M.R.C.P.

Senior Registrar, Department of Clinical Medicine, the General Infirmary at Leeds

AND

MAXWELL TELLING, D.M., F.R.C.P.

Assistant Physician, the General Infirmary at Leeds

The lesion of lymphangitis carcinomatosa has been known for over a century. First mentioned by Andral (1829), it was later reported by Virchow (1855), and then by Demme (1858), who described seven instances of a condition characterized by marked dyspnoea and a rapidly fatal issue, necropsy revealing wide dissemination of cancerous nodules in lungs and pleurae. Troisier (1873) gave the first fundamental account of the lesions and introduced the term "carcinomatous lymphangitis."

Generalized cancerous permeation of the pulmonary lymphatics is much rarer than the nodular, solid, or linear metastases more usually found, but it gives rise to a far more striking clinical picture, characterized by severe progressive unrelenting dyspnoea. Though the malignant nature of the condition is often appreciated, the site of the primary growth may not be recognized before death. It is in this group of patients that difficulty in diagnosis arises, rather than in those who develop respiratory symptoms while under observation for known malignant disease. The purpose of this paper is to report two new case histories, to discuss the clinical and pathological problems, and to review the literature.

Case 1

A housewife aged 54 was admitted to the General Infirmary at Leeds on August 4, 1950. She had always been healthy, but during the past two to three months she thought she had been losing a little weight, and in the past few weeks had begun to be short of breath on exertion. Two weeks before admission she had a slight cough and wheezing and her dyspnoea increased. When first seen on August 3 she was unable to give a detailed history owing to extreme dyspnoea, and unfortunately she had left her usual private doctor the day before because of his inability to relieve her distress. Apparently she had had a mild digestive upset at Christmas, 1949, characterized by transient anorexia and vomiting, which was ascribed at the time to dietetic indiscretion. In the past few days there had been infrequent vomiting of fluids.

On admission she was ill, cyanosed, markedly wasted, and in considerable respiratory distress. Apart from slight oedema of the feet, abnormal physical signs were confined to the chest, examination of which revealed bilateral pleural effusions, rales, and scattered rhonchi throughout both lungs.

The radiological appearances are shown in Fig. 1. The blood count was normal, and an electrocardiogram showed only left axis deviation. Aspiration produced an orange-coloured fluid which later became haemorrhagic, containing an excess of lymphocytes but no malignant cells. No organisms were seen and the fluid was sterile.

The normal cardiac findings, the gross dyspnoea, marked weight loss, minimal oedema, and absence of ascites, together with the radiological appearances of the lungs, all pointed to malignant permeation of the lungs from an unknown primary source: the complete failure of all treatment added further confirmation.

The patient was given a high protein diet, prophylactic penicillin, and sedation and oxygen as needed. The effusions required repeated tapping, some 15 pints (8.5 litres) being removed in five weeks, though little improvement followed any of the aspirations. Digitalization had no effect. On August 24 she was seen by Mr. G. H. Wooler, who suggested that, in view of the gastric episode the previous Christmas and the occasional vomiting before admission, the primary growth might be in the stomach. Her general condition gradually worsened, respirations averaging 30 and pulse rate 110; dyspnoea finally became extreme, unrelieved by aspirations and hardly influenced by oxygen. Cyanosis persisted to her death on September 9, five weeks after admission. There was no evidence of right heart failure and she was always afebrile.

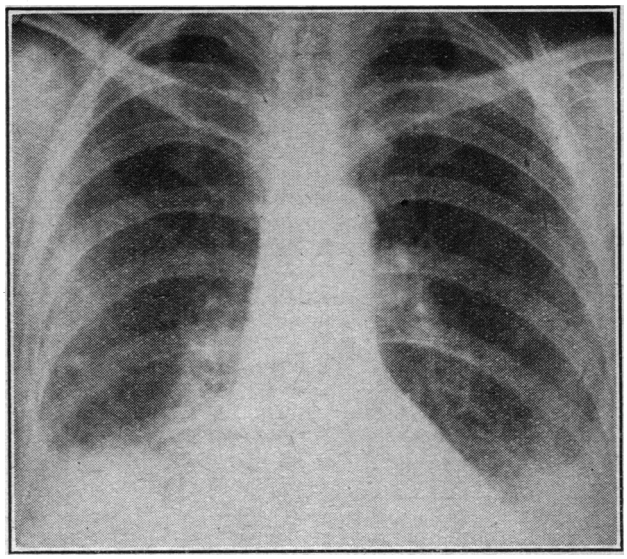

FIG. 1.—Note lower zones obscured by residual effusions, and that mottling, uniformly distributed throughout both lungs, follows a clear-cut reticular pattern. A suggestion of linear striation is seen at the left base, just above the effusion.

Post-mortem Examination

There was a malignant ulcer 3 in. (7.5 cm.) in diameter on the greater curvature of the stomach, immediately above the pylorus, extending across both anterior and posterior walls, with gross thickening of the adjacent mucosa and slight induration in the greater omentum. The pyloric glands on the greater curvature were enlarged and obviously invaded by growth.

The lungs were oedematous, with a peculiar reticular thickening, best appreciated by palpation, characteristic of cancerous permeation of the lung. Both pleural cavities were partly obliterated by dense fibrous adhesions, and each contained a large effusion of clear serous fluid. To the naked eye the hilar glands were normal.

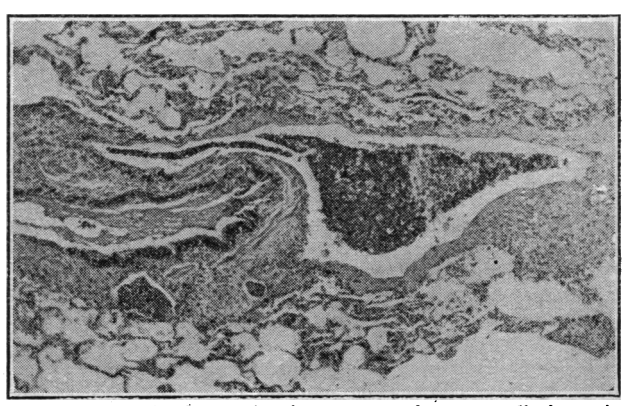

FIG. 2.—Case 1. Lung showing masses of cancer cells in peribronchial lymphatics and partly surrounding a collapsed bronchiole containing mucus.

Histological examination disclosed replacement of the gastric mucosa and muscularis mucosae by a layer of fibrinoid necrosis. Cancerous acini were irregularly scattered through the granulating submucosa, and lymphatic permeation was present in the serous coats, though in the muscle layers only beginning invasion by direct extension of growth was seen. An adjacent gland was largely replaced by growth, which in one part permeated an afferent sinus. The lungs showed diffuse permeation of the perivascular lymphatics by growth, and there were occasional groups of tumour cells within the alveoli (Fig. 2). Where the permeation was heavy there was surrounding fibrosis. Some of the smaller arteries, which were surrounded by cuffs of cancer cells in expanded perivascular lymphatics, were partly occluded by endarteritis obliterans (Fig. 3). On the visceral pleura there was fibrous thickening in relation to the malignant infiltration, and a superficial layer of organizing fibrinous exudate. The hilar glands were not examined microscopically.

FIG. 3.—Case 1. Lung showing a small artery partly occluded by endarteritis obliterans and almost surrounded by a cuff of cancer cells in an expanded perivascular lymphatic channel.

Case 2

A hand sewer aged 34 was seen privately on October 4, 1950. She stated that for four to five years she had had pain in the epigastrium immediately after meals which was relieved by alkalis. For the past two to three months she had been losing weight and appetite and energy, and had noticed a sensation of food sticking in the lower part of her chest, especially solids. In the past few weeks she had become short of breath on exertion, and had been vomiting occasionally in the past few days.

Examination revealed a well-nourished woman with a well-marked aortic diastolic and a short mitral systolic murmur; the heart was otherwise normal, and the blood pressure was 140/90. She was not dyspnoeic at rest. There were no enlarged glands and she was not anaemic. A lump very suggestive of an enlarged spleen could be felt in the left hypochondrium. She was referred to the out-patient department for further investigation, which on October 6 revealed a normal blood picture, negative Wassermann reaction, and an E.S.R. of 15 mm. (Westergren's method); radiological examination of the alimentary tract and chest was arranged.

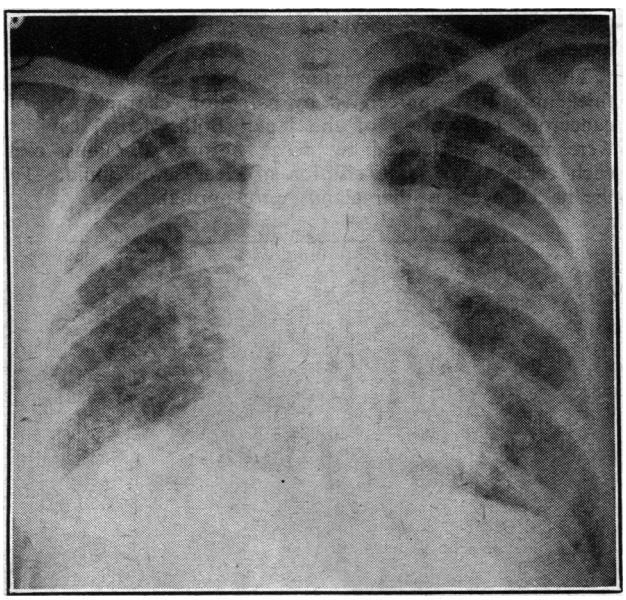

FIG. 4.—Note considerable mottling of coarse reticular type throughout both lungs and small effusion at right base. Opposite anterior end of third right rib are two clear linear streaks. Linear radiation from each hilum is moderately well shown and the hilar shadows are more prominent than usual.

She next attended on November 10, when she was seen by a deputy. She was dyspnoeic at rest, with a persistent non-productive cough, some generalized bronchial spasm, and a small right basal effusion. She said she had spent most of the five weeks since her first attendance in bed owing to her dyspnoea, which had become steadily worse. Radiological examination had been carried out on November 8, and the heart, oesophagus, stomach, and duodenum appeared to be normal; the appearance of the lungs is shown in Fig. 4. A further appointment was arranged, but owing to great increase in breathlessness she had to be admitted as an emergency on November 22.

The clinical picture on admission was dominated by her respiratory embarrassment. Her temperature was 100.2° F. (37.9° C.), pulse 112, and respirations 40. She was cyanosed, but there was no evidence of raised venous pressure or of oedema. In the chest there were widespread rhonchi and medium rales, and a right basal effusion. The cardiac and abdominal findings were unchanged. She was nursed in an oxygen tent, but despite this and treatment with penicillin and antispasmodics her condition rapidly deteriorated, cyanosis becoming more marked and dyspnoea extreme, until she died on November 25.

Post-mortem Examination

The stomach contained a large carcinoma involving the whole posterior wall of the body, and was fixed to the spleen and the tail of the pancreas by adhesions surrounding a mass of enlarged cancerous glands in the greater omentum: 3 in. (7.5 cm.) of the tail of the pancreas was replaced by growth, and the under-surface of the left dome of the diaphragm was studded with cancerous nodules.

The lungs weighed 3½ lb. (1.6 kg.), the right, which showed marked malignant sclerosis of the hilum, being smaller than the left. There was diffuse thickening of the bronchial wall of both lungs and on palpation the parenchyma displayed a firmness which suggested malignant permeation. The right pleural cavity contained a quart (1.1 litres) of serous fluid, and on the visceral pleurae were many diffuse plaques of growth, mainly on the pericardial surface. The hilar glands were invaded by growth. Apart from a bicuspid aortic valve there were no other abnormal findings.

Histological examination revealed a mucoid carcinoma of the stomach composed chiefly of spheroidal cells with some signet-ring forms. The tumour was mainly submucous, but widespread lymphatic permeation in the serous coat had taken place. In the lungs there was widespread peribronchial and perivascular invasion by mucoid carcinoma, especially notable in the pleural and the perivascular subpleural lymphatic channels. Section of a hilar gland showed it to be invaded by widely separated anaplastic tumour cells penetrating the gland capsule.

Radiological Appearances

A full discussion is beyond the scope of this paper, but, in brief, the radiological appearances depend upon a varying combination of (1) linear striation converging radially on the hilum; (2) granular or nodular mottling; (3) reticulation, often very well shown at the periphery; and (4) hilar glandular enlargement. They may be further modified by effusion, atelectasis, or congestive heart failure. The following brief case report illustrates some of the difficulties of diagnosis.

A coal-miner aged 40 was found to have a large carcinoma of the stomach. Radiology of the chest revealed a granular pattern which normally would have been ascribed to his occupation. The presence of a known carcinoma of

the stomach raised the possibility of lymphangitis carcinomatosa, but this was not confirmed at necropsy, when only typical anthracosis was found.

Discussion

By the time of their admission to hospital both these patients were incapacitated by dyspnoea. This was so severe, and its development so rapid, that attention was at once directed to a primary pulmonary cause. Though respiratory symptoms are not infrequently manifestations of malignant disease arising elsewhere than in the lungs, the clinical presentation described above is by no means common. The usual primary sites of growth which give rise to diffuse pulmonary lymphatic permeation are the stomach, bronchus, breast, prostate, and pancreas. Lymphangitis carcinomatosa may precede or obscure or dominate any local symptoms and present as a diagnostic problem in dyspnoea, as in our two patients. It may also occur during the evolution of a growth which has already been identified during life, in which case no clinical problem arises, as in Wu's (1936) 5 personal examples. Wu found in his analysis of 54 examples that a rather younger age group than usual was involved, the stomach being the site of the primary growth in about 75%, the bronchus in some 10%; we believe the proportion of bronchogenic cancer to be rather greater. We feel it useful as well as justifiable to distinguish sharply between these two groups.

Our clinical and radiological findings agree with those of other observers, notably Mendeloff (1945), who pointed out that severe and unremitting dyspnoea is the most common and distressing complaint of these patients. Boccard's (1925) graphic description of "la forme asphyxiante aiguë de la carcinose secondaire du poumon" is well justified. Neither of Mendeloff's two patients had any symptoms or signs referable to the primary site of the tumour. Our second patient had symptoms sufficient to warrant a barium examination of the stomach (with negative results), but no such lead existed in the first. One difficulty in the clinical appraisal of these patients is that general symptoms such as weight loss, weakness, and anorexia, which might in other circumstances be attributed to malignancy, can well be regarded as a secondary effect of the distress induced by severe dyspnoea.

Though the onset of symptoms is often insidious, it may be rapid and dramatic. It may also be precipitated by or occur simultaneously with an upper respiratory infection. In an interesting example reported by Gaines (1935), the initial symptoms of cough and dyspnoea followed and were considered attributable to the inhalation of large quantities of dust. The physical signs are usually slight in proportion to the degree of dyspnoea, mostly consisting of scattered rales and rhonchi, poor respiratory excursion, and sometimes pleural effusion. Asthmatic wheezing is common and was a striking feature of the cases of Mendeloff and of Sweigert *et al.* (1947). Right heart failure may be evident in those patients in whom pulmonary endarteritis has developed with resulting pulmonary hypertension, and Greenspan (1934) published an account of four patients showing carcinomatous endarteritis, two of whom had died with evidence of rapidly progressive right heart failure.

The diagnosis is suggested by the combination of severe dyspnoea out of proportion to the physical signs, a normal heart size, the absence of the usual signs of congestive heart failure, and the characteristic radiological picture. The electrocardiographic findings are of no diagnostic help. Marked loss of weight, if present, is suggestive, and the complete failure of all treatment affords valuable confirmation.

Unfortunately the hilar glands in Case 1 were not examined microscopically: most reports stress their almost constant involvement and a tendency of the growth to prefer lymphatic dissemination. The most satisfactory explanation of the path of dissemination is that of Von Meyenburg (quoted by Jarcho, 1936), which is favoured by most authors. He suggested a retrograde permeation of the pulmonary lymphatics after involvement of the hilar lymph nodes. The preponderance of gastric cancer as the primary tumour is probably an expression not only of the high incidence of cancer in this organ but also of the fact that the lymphatic connexions between its regional lymph nodes and those of the lungs are comparatively short and direct (Wu, 1936). Nevertheless, neither primary blood spread (via the thoracic duct and right heart) nor pleural metastasis with final invasion of the pulmonary lymphatics can be discounted, though both paths seem unnecessarily complicated.

Obliterative changes in the pulmonary arteries are a feature of the histology of Case 1 and of eight of Wu's (1936) patients. The histological changes are mainly of two types—one thrombotic with subsequent organization, the other a true endarteritis. Occasionally the processes are combined. Greenspan (1934) regards these changes as an effect of the perivascular lymphatic permeation; but, while this is widespread, arterial changes may be scanty in relation to it, and some other explanation would seem to be required. Wu believes that the intravascular deposition of carcinoma cells plays an important part in the genesis of the obliterative changes. True endarteritis with intimal proliferation may arise as a result of thrombotic blockage of the lumen elsewhere in the affected vessel, with consequent reduction in the blood flow, or it may be caused by a direct toxic effect of the cancer cells. There is no doubt that generalized cancerous permeation of the pulmonary lymphatics, when associated with obliterative changes in the pulmonary arteries, can simulate the clinical picture of Ayerza's disease, in which dyspnoea and cyanosis are associated with hypertrophy of the right heart. Montgomery (1935), reviewing the literature, stated his opinion that, while the clinical features of Ayerza's disease are clear-cut, the underlying pathological processes may vary widely, and suggested the use of the term "Ayerza's syndrome."

Summary

The case histories of two patients with primary carcinoma of the stomach and generalized carcinomatous permeation of the pulmonary lymphatics are reported. The presenting symptom was severe and progressive dyspnoea, which dominated the clinical picture and overshadowed other evidence of malignant disease.

The clinical and pathological features of the condition are discussed and the literature is briefly reviewed.

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According to Lord Milner of Leeds, the name "sanitary inspector" has led to misconception. "The man in the street imagines that a sanitary inspector is a man who spends most of his time examining the drains, occasionally samples the milk, and generally does a number of disagreeable but necessary jobs." Lord Milner was delivering the presidential address at the Sanitary Inspectors' Association's conference at Brighton. He went on to enumerate some of the names which had been tried in the past. Among these were "sanitary police," "sanitarists," "inspectors of nuisances," and "sanitationists." The American version, "sanitarian," had not found much favour in this country (*Manchester Guardian*, September 10).