Circulatory Failure in Metastatic Carcinoma of the Lung

A Physiologic and Pathologic Study of Its Pathogenesis

By Ole Storstein, M.D.

Four cases of extensive metastatic pulmonary carcinomatosis have been studied from the point of view of hemodynamics (cardiac catheterization) and pathology in order to evaluate the various factors in the pathogenesis of the subacute form of cor pulmonale. The author stresses the importance of distinguishing between the extensive destruction of lung tissue, leading to anoxemia, and the invasion of lung vessels by cancer cells, leading to pulmonary arterial hypertension and later to failure of the right ventricle.

Of the two forms of cor pulmonale, acute and chronic, the former is associated with pulmonary embolism, the latter with chronic disease of the lungs, emphysema, chronic bronchitis, bronchiectasis, bronchial asthma, pulmonary tuberculosis, silicosis and Boeck's sarcoid; it may also be associated with recurrent attacks of pulmonary embolism, with that rare condition known as "primary pulmonary arterial hypertension" and with kyphoscoliosis. There is also an intermediate form, described as subacute cor pulmonale in which the disease lasts from nine days to two months. This form is caused by carcinomatous metastases to the lungs.

This condition may develop in various ways:

1. The embolic form, with cancer cell emboli to the small arteries of the lungs, and thrombosis and occlusion of their lumen.

2. Carcinomatous endarteritis of the vessels of the lung. Tumor cells in the perivascular lymphatic vessels provoke a varying degree of obliteration of the small arteries and arterioles of the lungs, partly by compression of the vessels and the direct invasion of the adventitia and media by cancer cells, partly by hyperplasia of the intima resulting from irritation by the surrounding cancer cells, and finally, by the formation of thrombi on the hyperplastic intima.

3. The suffocating form of carcinomatous lymphangitis. Here there is an extensive and diffuse invasion of the lymphatic vessels of the lungs by cancer cells, with compression of the alveoli and bronchioles but without involvement of the lung vessels.

In most cases the original source of the metastases is carcinoma of the stomach, but they may also originate in carcinoma of the colon, of the pancreas, of the breast, or a chorion epithelioma. The metastases to the lungs may travel via the hepatic vein and inferior vena cava, but most frequently their route is via the thoracic duct to the pulmonary lymphatic vessels or to the superior vena cava.

The clinical picture is characterized by the rapid development of severe dyspnea and cyanosis, followed later by signs of failure of the right ventricle in patients without any previous signs of disease of the lungs or heart. The signs referable to the lungs consist of a certain amount of dyspnea, often in the form of tachypnea, cough, attacks of suffocation on change of position, and cyanosis. The signs referable to the circulatory system are a low blood pressure, tachycardia, irregular action of the heart, enlargement of the liver and edema. Attacks of collapse have been described with a further fall of blood pressure, tachycardia of 150, and tachypnea of 54. The clinical findings over the heart and lungs are rather slight; there are some rales over the lungs, the heart sounds are weak, and occasionally there may be a gallop rhythm over the lower part of the sternum.

It is common for the primary carcinoma to
provoked signs which betray it, but the disease often comes as a surprise at postmortem examination, particularly in the case of carcinoma of the stomach. Occasionally the primary seat of the malignancy cannot be found at autopsy. The French in particular have emphasized the importance of radiologic examination of the lungs, which may reveal a picture characteristic of the suffocating type, where straight striae and strands cross each other and invade the pulmonary fields. But these radiologic signs are often lacking.

Most authors emphasize cyanosis as an essential feature of the clinical picture. But no analyses of the oxygen content of the arterial blood were made until McMichael demonstrated a very low oxygen saturation of 78 per cent of the arterial blood in a patient with a suffocating form of carcinomatous lymphangitis of the lungs. In the same case McMichael found a high cardiac output of 7 liters per minute and a pressure in the right auricle of 2 to 3 cm. H₂O above the normal.

Apart from McMichael's observation and the demonstration by Baldwin, Courmand and Richards of an alveolorespiratory insufficiency in 2 cases of carcinomatous lymphangitis of the lungs, no studies have been found by the author of the circulatory disturbances produced by this condition. This study reports 4 cases of extensive carcinomatous metastases to the lungs. In these cases we have estimated the oxygen saturation of the arterial blood and in 2 of them we have also studied the circulation more closely by catheterization of the heart.

Case Reports

Case 1. The first patient was a woman of 36, who had been operated on in October, 1946, for carcinoma of the breast with metastatic nodules in the lymphatic system. She had been given postoperative high voltage x-ray treatment. Since the spring of 1947 there had been progressive lassitude and fatigue, and she had been confined to bed since March 1, 1948. She was treated at the Medical Department of Haukeland Hospital from April 29 to June 14, 1948. While she was in hospital, the clinical picture was characterized by tachycardia at a rate of about 140, low blood pressure (85/65), dyspnea (30), clamminess of the skin, pallor and a greyish-blue color of the skin, and bouts of coughing. Oxygen, which had to be given continuously, had a definite palliative effect. A skiagram showed an effusion in the right sinus, but no definite parenchymatous shadows. Electrocardiographic examination showed normal conditions apart from tachycardia. The oxygen saturation of the arterial blood was much reduced (table 1).

The postmortem examination (Professor Waaler) showed a pleural effusion on both sides (1500 cc. on the right side, 600 cc. on the left). Numerous white, firm nodules, the size of a pin head, were scattered over the pleura and parietal pericardium and the incised surfaces of the lungs, and were also found in the liver and osseous system. The heart weighed 300 Gm. and the wall of the right ventricle was

![Fig. 1. Medium-sized lung vessel containing small groups of tumor cells in the wall. No thickening of the intima. (X 110).

Slightly hypertrophied (0.5 cm.). A microscopic examination showed extensive atelectasis of the lungs and diffuse infiltration, with atypical epithelial cells forming small and large nodules, particularly in the pleura. These lesions represented extensive metastases to the pleura and lungs, combined with dissemination of carcinoma cells along the lymphatic channels. In the adventitia of the arteries small islands of atypical epithelium (fig. 1) could be seen, but there was no proliferation of the intima or formation of thrombi.

Case 2. The second patient was a 57 year old man, who during the last three months had shown great lassitude and fatigue, and during the last four...
weeks had had a cough with blood-stained expectoration and vomiting. While in hospital, between June 17 and 29, 1948, his temperature was about 38.5° C. He suffered from repeated hematemesis, and the feces constantly contained occult blood. There was progressive anemia. The electrocardiogram was normal except for a negative T wave in leads I and II. Radiologic examination showed miliary shadows in both lungs. Because of his condition no barium test meal was given. The arterial oxygen saturation was normal (table 1).

The postmortem examination (Professor Waaler) showed a tumor of the stomach, measuring about 6 cm. in diameter. On section, the lungs, liver, pancreas and heart showed white nodules ranging from the size of a pea to that of a nut. The right pleural cavity contained 300 cc. and the left pleural cavity 500 cc. of fluid. The tumor of the stomach proved on microscopic examination to be an adenocarcinoma, and it was of this that the above-mentioned nodules consisted. In a few places there was atheromatous thickening of the intima of the medium-sized blood vessels of the lungs with plentiful collagen and subendothelial connective tissue. The changes in the blood vessels were, however, only moderately extensive. Some of the smaller arteries presented infiltration in the perivascular lymphatic spaces by tumor cells, with proliferation of the intima and closure of the blood vessels (fig. 2). These changes were not very extensive.

Case 3. The third patient was a man of 48, who became ill in the middle of May 1949. Cough and successive small hemoptyses as well as emaciation were the chief evidences of his illness. While in hospital, between July 15 and 29, 1949, he was very weak. His complexion was a cadaver-like pale grey. There was tachycardia of about 120. Blood pressure was 110/65. The liver was palpable 6 cm. below the costal arch. A radiologic examination showed a diffuse, finely spotted infiltration in both lungs. There was no occult blood in the feces. There was considerable reduction of the arterial oxygen saturation (table 1), the cardiac output was normal, and there was definite hypertension in the pulmonary artery (table 2).

The postmortem examination (Professor Waaler) showed in the posterior wall of the stomach a sclerotic area about the size of a penny, which was covered by a smooth, atrophic mucous membrane. In direct continuity with this area, on the serous side of the stomach, behind the peritoneum, were several firm and elastic nodules at least as large as a prune. On section numerous nodules were found in the lungs, under the pleura and in the spinal column. The heart weighed 310 Gm., and the wall of the slightly hypertrophied right ventricle measured 0.4 cm. Microscopic examination showed an adeno-

<table>
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<th>Patient</th>
<th>Age</th>
<th>Date</th>
<th>Ox capacity, Vol. per cent</th>
<th>Arterial oxygen content Before O₂ resp.</th>
<th>After 10 min. 100% O₂</th>
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<td></td>
<td></td>
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<td>Vol. per cent</td>
<td>Per cent sat</td>
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<td>1. S. H.</td>
<td>36</td>
<td>May 24, 1948</td>
<td>20.09</td>
<td>10.27</td>
<td>51.1</td>
</tr>
<tr>
<td></td>
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<td>June 11, 1948</td>
<td>17.43</td>
<td>7.2</td>
<td>41.3</td>
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<td>2. H. B.</td>
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<td>June 28, 1948</td>
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<td>14.04</td>
<td>10.93</td>
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<td>69</td>
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<td>11.73</td>
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<td>March 20, 1950</td>
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<td>5.85</td>
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FIG. 2. Small arteriole in the lung with proliferation of the intima and thrombosis. (× 110).
carcinoma with many peculiarly shaped nuclei and numerous mitoses in the stomach wall. The blood vessels were infiltrated by the tumor, and the structure of the nodules found in the lungs was of the same type as that of the tumor in the stomach wall. The perivascular lymphatic spaces and the adventitia and media of the blood vessels in the lungs were infiltrated by the tumor. The small arteries showed extensive endarteritic changes, with some thrombosis and complete blocking of the lumen, which in some places was much narrowed (fig. 3). There was also considerable tumor cell infiltration of the arteries and veins of the lungs (fig. 4), as well as the smallest blood vessels in the lungs (fig. 5).

Case 4. The fourth patient was a woman of 68, who had been operated on for carcinoma of the breast in October, 1948, and had been given postoperative high voltage x-ray treatment. There was a local recurrence of the disease, and for this she was given radiologic treatment in December, 1949.

At the beginning of 1950 she was confined to bed. She was treated in the hospital between February 14 and March 25, 1950. Her complexion was grey with a hint of cyanosis most in evidence in her nails. The pulse rate was 120 and regular; blood pressure, 115/65; and respiration, 32 and labored. She coughed incessantly and needed oxygen continuously. An electrocardiographic examination showed tachycardia and flat T waves in leads I and II. Radiologic examination of the chest on admission to the hospital showed densely grouped, small, parenchymatous shadows in both lungs. A pleural effusion which developed on the left side was repeatedly evacuated. The arterial oxygen saturation was much reduced (table 1); the cardiac output was normal; and there was no definite hypertension of the pulmonary artery (table 2).

The postmortem examination (Professor Waaler) showed recurrence of the disease at the site of amputation of the breast. The left pleural cavity

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date</th>
<th>A-V O2 diff</th>
<th>O2 consumpt. ml/min</th>
<th>CO L/min</th>
<th>Cl L/min/M^2</th>
<th>Pressure mm Hg</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right aur.</td>
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<tr>
<td>3. B. L</td>
<td>July 21, 1949</td>
<td>43.5</td>
<td>assumed 220</td>
<td>5.0</td>
<td>3.1</td>
<td>1.5/ + 3.5</td>
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<tr>
<td>4. O. O</td>
<td>Jan. 26, 1950</td>
<td>44.5</td>
<td>173</td>
<td>4.0</td>
<td>2.5</td>
<td>25/ + 3</td>
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Fig. 3. Tumor infiltration in a small lung vessel. Intense thickening of the vessel wall. (X 220).

Fig. 4. Medium-sized lung vessel filled by tumor cells. (X 110).
contained 1000 cc. of fluid. The visceral and parietal pleura, the lungs on section, the parietal pericardium, the liver and the osseous system were studded with numerous firm, greyish-white nodules. There were also enlarged lymph nodules in the hilar region of the lungs and in the liver. The heart weighed 220 Gm., and the wall of the right ventricle was normal, measuring 0.3 cm. A microscopic examination of sections from the lungs showed a diffuse infiltration by nodules of various sizes, consisting of atypical epithelial cells. Numerous lymphatic spaces were packed with tumor cells. The thickened pleura showed infiltration by tumor cells. At a few sites moderately large vessels had been infiltrated by the malignant tissue, and some vessels of the lungs were filled with tumor thrombi.

These cases illustrate various types and degrees of carcinomatous metastases to the lungs. It is probable that the first case belongs to Costedoat's suffocative form,\(^3\) with diffuse invasion of the lymphatic vessels of the lungs by a finely nodular scirrhous type of lesion. The nodules were barely visible to the naked eye.

The second case presented changes in the blood vessels of the lungs corresponding to Greenspan's description\(^4\) of carcinomatous endarteritis. But the changes were not extensive, nor was there any great invasion of the lungs by carcinoma cells. This fact probably explains the normal arterial oxygen saturation. Neither was there any clinical evidence of increased pressure in the pulmonary circulation or failure of the right ventricle. These observations emphasize the quantitative factor in the disease; there is no rise of pressure in the pulmonary artery until there has been extensive destruction of the tissues surrounding the blood vessels of the lungs. Acute experiments, such as those carried out by Fineberg and Wiggers,\(^2\) who gradually compressed the pulmonary arteries of dogs, showed that the right ventricle of the heart could compensate for the narrowing of the lumen of the arteries until it had been decreased to 60 per cent of the normal. Only after this limit had been passed did failure of the right ventricle develop rapidly.

In the third case, extensive vascular changes consisted partly of carcinomatous endarteritis and partly of a direct invasion and obstruction of the small arteries of the lungs with carcinoma cell emboli. In conformity with Schmidt's description,\(^3\) this patient presented during life considerable hypertension of the pulmonary artery and signs of failure of the right ventricle with enlargement of the liver.

The fourth patient presented extensive infiltration of the lungs, particularly the lymphatic channels and the pleura, with tumor cells. There were also some changes in the blood vessels, but they were not extensive enough to provoke any definite hypertension of the pulmonary artery. The dominant feature of this case was the destruction of lung tissue and the compression of the bronchi, resulting in a reduction of the respiratory function of the lungs.

**FIG. 5.** Small lung vessel filled by tumor cells. (X 220).

**DISCUSSION**

With regard to the pathogenesis of these conditions, there are two features which should be kept more distinct from each other than has hitherto been the case in publications on the topic. One of these features is cyanosis and diminished arterial oxygen saturation; the other is hypertension of the pulmonary artery with hypertrophy of the right ventricle.
The cyanosis belongs to the type which has been described as "heliotrope cyanosis." The patient's color is pale and greyish, with a hint of cyanosis, most clearly visible in the nails. It is not striking, and the arterial oxygen saturation often comes as a surprise; in 2 of the present cases it was reduced to 40 per cent. The reduced arterial oxygen saturation is the measure of the reduction of the alveolorespiratory function of the lungs. Frequently there is at the same time a reduction of the ventilatory function, with severe dyspnea as the most important symptom. The carcinoma cells invade the lymphatic vessels of the lungs, compressing the alveoli and bronchioles in such a way that the respiratory exchange of gases is hampered as a result of destruction of the respiratory membrane. Anoxemia will therefore be particularly prominent in the suffocative form of the disease, where an extensive invasion by carcinoma cells takes place through the lymphatic channels. The exchange of gases in the embolic form of the disease with carcinomatous endarteritis will also be hampered because of obliteration of the small vessels of the lungs.

In case 3, the pressure in the pulmonary artery was considerably raised, the mean pressure being 23.5 mm. Hg (normal pressures with our technic do not go above 12 mm.); the mean pressure in the right auricle was normal. In conformity with these pressures the arterioles and small arteries of the lungs were found to have been to a considerable extent obliterated.

The most important cause of hypertension of the pulmonary artery in diseases of the lungs is increased pulmonary resistance caused by the destruction of arterioles and capillaries. As already pointed out, the arteries of the lungs have to undergo considerable compression before the right ventricle begins to fail. We may assume, however, that before this stage of failure is reached there is a stage of compensation with a rise of pressure in the pulmonary circulation.

There are also functional factors responsible for hypertension in the pulmonary artery, the most important being the relationship between the blood flow through the lungs and the capacity of the vascular bed. When the vascular bed is normal, the circulation of blood can be trebled without the pressure in the pulmonary artery being raised; but when the vessels of the lungs are diseased, a slight increase of blood flow will provoke hypertension. These patients often present a raised cardiac output and fall into the group with "high output failure." Our 2 patients presented a normal cardiac output, of 5 and 4 liters per minute respectively. McMichael maintains that the cardiac output falls in the final stage of cor pulmonale. Motley and associates have shown that brief anoxemia in man may provoke hypertension of the pulmonary artery, an observation which agrees with the experimental observations on the cat by v. Euler and Liljestrand. They found that a lack of oxygen stimulates contraction of the blood vessels of the lungs. In chronic pulmonary disease Cournand and associates have found a close correlation between the arterial oxygen saturation and pulmonary arterial pressure. It was therefore surprising that the pressure was not higher in case 4, in which there was considerable anoxemia.

In view of these considerations the conclusion may be drawn that in these patients it is mainly the anatomic changes in the blood vessels of the lungs, with a reduction of the vascular bed, which provoke the hypertension in the pulmonary artery.

The two factors, anoxemia and hypertension of the pulmonary artery, acting to some extent independently and to some extent in conjunction with each other, lead to hypertrophy and dilatation of the right ventricle, which finally fails, as described in the terminal stage of subacute cor pulmonale.

**Summary**

In 4 cases of carcinomatous metastases to the lungs (2 from primary carcinoma of the stomach, undiagnosed during life, and 2 from cancer of the breast) there were 3 in which the arterial oxygen saturation was reduced, being in 2 cases as low as 40 per cent.

In one of these cases, hypertension of the pulmonary artery and signs of failure of the right ventricle were also observed.

In the pathogenesis of this condition it is important to distinguish between the anoxemia, which is due to destruction of the respiratory
surface of the lungs, and the hypertension of the pulmonary artery, which is due to invasion of the arteries of the lungs by cancer cells. In the 3 cases with anoxemia, extensive destruction of the pulmonary tissue was observed. The patient with hypertension of the pulmonary artery proved to have carcinomatous endarteritis in the arteries of the lungs.

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