Microscopic Pulmonary Tumoral Embolism and Subacute Cor Pulmonale as the First Clinical Signs of Cancer

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Acta Oncologica Vol. 38, No. 8, pp. 1116–1118, 1999

Received 9 November 1998
Accepted 24 February 1999

People with cancer have increased risk of pulmonary thromboembolism. Microscopic tumour embolism followed by pulmonary hypertension and, occasionally, subacute cor pulmonale, is a rare and under-diagnosed presentation. In exceptional cases the respiratory symptoms mentioned above are the first signs of cancer. The correct evaluation of this clinical picture is essential in order to avoid aggressive therapies. We describe a case of microscopic pulmonary tumour embolism (MPTE) as the first sign of gastric cancer and present a review, carried out using MedLine, of the literature related to this atypical clinical presentation. The absence of liver involvement in primary neoplasms other than hepatocarcinoma is also noted.

Case report. A 78-year-old woman presented with weight loss, anorexia and exertional dyspnoea for the previous 4 months. One month before admission she underwent a physical examination, EKG, chest x-ray and abdominal echography and no abnormality was noted. Blood tests showed mild anaemia. The patient did not smoke or consume alcohol and was taking omeprazol therapy due to a hiatus hernia diagnosed 8 years previously.

On admission, the patient's blood pressure was 105/75 mmHg, temperature 36.4°C and respiration rate 36 breaths/min. Physical examination revealed acrocyanosis and a grade 3/6 multifocal holosystolic murmur. Her jugular venous pressure was elevated and the hepato-jugular reflux was present. No abnormalities were found in the lower extremities.

Laboratory data were normal, except for a haemoglobin concentration of 11.7 g/dL and an haematocrit of 36% with a mean corpuscular volume of 86 fL and a lactate dehydrogenase value of 12 microkat/L. The level of acute phase reactants was increased and liver function tests showed mild cytolysis. Basal arterial blood gases evidenced pH 7.45, 58 mmHg pO_2, 24 mmHg pCO_2, 17 mEq/L bicarbonate and 91% O_2 saturation. Serum carcinoembryonic antigen and serum alpha-foetoprotein levels were normal.

Chest x-ray demonstrated slight prominent hilar shadows, diffuse bilateral interstitial pattern and Kerley B lines. An electrocardiogram revealed sinus tachycardia at a rate of 110 **(Author – units?),** with incomplete right-bundle-branch block and a $S_1Q_3T_3$ pattern. Echocardiogram showed a dilated right ventricle and a pulmonary arterial pressure of 100–105 mmHg. A lung perfusion scan and pulmonary angiogram showed no signs of pulmonary embolization. The abdominal ultrasonographic examination revealed absence of intra-abdominal masses.

The patient's clinical condition worsened, with increased dyspnoea, systemic hypotension and oliguria. Arterial blood gases (0.50 FI, O_2) were 43 mmHg pO_2 and 30 mmHg pCO_2. Orotracheal intubation, mechanical ventilatory support and anticoagulant therapy with heparin were initiated immediately. Pulmonary artery catheterization revealed a central venous pressure of 15 mmHg, a pulmonary-capillary wedge pressure of 12 mmHg and a pulmonary artery pressure of 80/40 mmHg. On day 6, despite supportive measures, the patient died.

Autopsy revealed mucinic gastric adenocarcinoma with local and mediastinal metastatic lymph nodes. Lymphangitic carcinomatosis was also present in the pulmonary, abdominal and pelvic regions. Examination of the pulmonary arterioles showed multiple tumour emboli, with thrombi occasionally containing entrapped tumour cells; fibrocellular intimal proliferation was also observed. The liver was congestive; histologically, the hepatic cells and interstitium were oedematous and no evidence of tumour was found.

Discussion. Patients with cancer can develop pulmonary embolism of either thrombotic or neoplastic origin by large tumour emboli or microemboli (1–3). MPTE is an under-diagnosed pathology (1, 2, 4), although it is a frequent cause of morbidity and mortality in cancer patients. Based on autopsy studies, the incidence of MPTE among solid neoplasms has been estimated to range from 2.4% to 26% (2, 3, 5), and in 1–8% of the diagnosed cases it was considered to be the cause of death.

The most frequent primary neoplasms in patients with MPTE are: gastric cancer, breast cancer and trophoblastic carcinoma (choriocarcinoma) (1–3, 5–7). Hepatocarcinoma (2, 3, 5–10), the most frequent neoplasm in other series (7), pancreas cancer (5–8, 11), lung cancer (1, 2, 6, 8, 12, 13) and prostate cancer (2, 3, 5, 8, 12, 13) are other frequent neoplasms. Histologically, adenocarcinoma is seen in 90% of the reported cases (8).

 ISSN 0284-186X

The most remarkable feature of the case described here is that MPTE, presenting as subacute cor pulmonale, constituted the initial manifestation of gastric neoplasm. Pulmonary tumour embolism may develop at any time in neoplastic patients, but is rarely the initial sign of the disease (see Table 1). Metastatic cells reach the pulmonary vessels. Most of them are destroyed intraluminally (1–3, 5, 8, 10), but some can reach the perivascular lymphatic vessels, where they originate parenchymal metastases. There is no difference in the clinical presentation of MPTE and isolated lymphangitis. However, isolated lymphangitis typically shows an insidious and longer clinical evolution that does not lead to cor pulmonale (6).

Table 1

Summary of data from cases of subacute cor pulmonale as the first manifestation of cancer

Year (reference)	Age (years)/ sex	Primary neoplasm (histology)	Metastases	Liver metastases	Clinical symptoms (duration)	Chest x-rays	EKG	Initial diagnosis	Microscopic examination
1980 (9)	63/M	Liver (hepatocarcinoma)	Endocardium, lungs, pleura, adrenal gland, lymph nodes	Primary multifocal hepatocarcinoma	Dyspnoea, RVF (13 months)	Basilar atelectasis	ND	CHF, pulmonary hypertension	Multiple microemboli
1980 (14)	27/F	Stomach (adenocarcinoma)	Lymph nodes, liver, ovary, vertebra cardiac and renal vessels	Yes	Flank pain (5 weeks), dyspnoea, dry cough (2 weeks), RVF	Prominent pulmonary arteries, interstitial pattern	Sinus tachycardia, right QRS axis	PTE	PTTM
1984 (10)	48/F	Liver (hepatocarcinoma)	Lungs, portal vein, splachnic venous bed	Large primary hepatocarcinoma	Dyspnoea, RVF (20 months)	Prominent pulmonary arteries	ND	Primary pulmonary hypertension	Multiple microemboli
1988 (15)	36/F	Stomach (adenocarcinoma)	Lymph nodes, adrenal gland, ovaries	No	Cough (2 months), hypocondrodynia (several weeks), dyspnoea, RVF	Prominent pulmonary arteries	Sinus tachycardia, right QRS axis	Pulmonary hypertension	PTTM
1990 (7)	ND/F	Liver (hepatocarcinoma)	ND	Primary hepato-carcinoma	Dyspnoea, RVF (ND)	Clear	Sinus tachycardia, right QRS axis	ND	Multiple microemboli
1990 (7)	ND/F	Liver (hepatocarcinoma)	ND	Primary hepato-carcinoma	Dyspnoea, RVF (ND)	Clear	Sinus tachycardia, right QRS axis	ND	Multiple microemboli
1990 (7)	ND/F	Pancreas (adenocarcinoma)	ND	ND	Dyspnoea, RVF (ND)	Clear	Sinus tachycardia, right QRS axis	ND	Multiple microemboli
1991 (5)	56/M	Liver (hepatocarcinoma)	ND	Primary multifocal hepato-carcinoma	Jaundice, abdominal pain, dyspnoea (several weeks), no RVF	Clear	right QRS axis, S_1Q_3 pattern	ND	Multiple microemboli
1992 (1)	51/M	Lung (adenocarcinoma)	Multiple	Yes	Dyspnoea, weakness (1 month), no RVF	Prominent pulmonary arteries	ND	Pulmonary hypertension, PTE	PTTM
1992 (1)	70/F	Ovary (endometriod)	ND	No	Dyspnoea, RVF (2 months)	Prominent pulmonary arteries	ND	CHF	PTTM
1994 (4)	62/F	Bilateral ovaries (undifferentiated)	Peritoneum	No	Respiratory distress (ND), RVF	Cardiomegaly	Sinus tachycardia, S_1Q_3 pattern	PTE, atypical pneumonia	PTTM
1997 (16)	37/F	Stomach (adenocarcinoma)	Lymph nodes, pancreas, ovaries	No	Dyspepsia, cough (1 month)	Clear	Sinus tachycardia	PTE	PTTM
Present case	78/F	Stomach (adenocarcinoma)	Disseminated adenopathy and lymphangitis	No	Toxic syndrome, dyspnoea (4 months), RVF	Prominent hili, interstitial pattern	Sinus tachycardia, S_1Q_3 pattern, right-bundle-branch block	PTE	PTTM

Abbreviations: CHF = congestive heart failure; ND = not done; PTE = pulmonary thromboembolism; PTTM = pulmonary tumour thrombotic microangiopathy; RVF = right ventricular failure.

It has previously been suggested that pancreas cancer and hepatocarcinoma may lead to lung metastases via the venous drainage system without liver involvement, while in other neoplasms, such as prostate, breast and stomach cancer, liver metastases are more typical, before systemic dissemination leads to development of lung metastases (1, 3). However, our review of 13 cases of cancer presenting as subacute cor pulmonale revealed that 8 out of the 13 cases were primary neoplasms other than hepatocarcinoma and only in 2 out of 8 of them involved the liver secondarily.

Subacute dyspnoea is the main complaint among patients with MPTE (1, 3, 5, 10), although up to 50% of the autopsied cases had no previous clinical signs (3, 5). Some patients may develop subacute cor pulmonale (6) associated with respiratory failure refractory to conventional treatment (2). Symptoms typically exceed signs (1, 2) and laboratory tests can show hypoxaemia and abnormal liver tests due to hepatic metastases (5).

Diagnosis of tumour embolism is more difficult than diagnosis of thrombotic pulmonary embolism and misdiagnosis may occur (1, 2, 4, 5, 7, 12). Open lung biopsy and transbronchial biopsy are the diagnostic procedures of choice (4, 13). Cytology sampling with a balloon catheter implanted in the pulmonary artery (Swan–Ganz catheter) has been used for detecting circulating tumour cells in patients with lymphangitis (8, 13).

Histological examination reveals alterations in the small and medium sized pulmonary arteries (1, 2, 4–6, 8), consisting of fibrocellular intimal proliferation with the concurrent presence of thrombi occasionally invaded by tumour cells. The term pulmonary tumour thrombotic microangiopathy has been suggested for this lesion (8) and it has not been detected in other organs (e.g. the kidney).

MPTE implies a worse prognosis than parenchymal metastases or lymphangitis because of the irreversible cardio-pulmonary alterations produced by MPTE (6).

In summary, the diagnosis of MPTE should be considered in those neoplastic patients who develop cor pulmonale. Most of these patients also show evidence of neoplasms in other organs, but in selected cases the clinical manifestations of pulmonary embolism could be the first sign of the disease, although there is no clinical evidence of liver involvement. Correct diagnosis is often difficult and is based on a high index of suspicion. It allows palliative therapy to be commenced without continuing aggressive diagnostic procedures.

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