Fatal microscopic pulmonary tumour embolisms in patients with breast cancer: Necessary knowledge for future medical practice

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ABSTRACT

Microscopic pulmonary tumour embolisms (MPTE) are a rare but life-threatening phenomenon in patients with a history of adenocarcinoma. Due to the nonspecific symptoms, diagnostic difficulty, and rapid progression, this condition is often fatal. We describe two patients who previously completed breast cancer treatment, and now present with fatal MPTE and we provide a comprehensive review of the literature.

KEYWORDS

Breast cancer, microscopic pulmonary tumour embolisms, metastatic disease

INTRODUCTION

Although pulmonary metastases are common in advanced breast cancer patients, microscopic pulmonary tumour embolisms (MPTE) are rarely diagnosed. When reaching the lungs, tumour cells escaped from the tumour vasculature can become trapped within pulmonary capillaries giving obstruction. In contrast to pulmonary thromboembolism, MPTE are not visible on a chest computed tomography angiography (CTA). Multiple occlusions of small vessels may produce pulmonary hypertension leading to right ventricular failure, ultimately resulting in death. Since the first description of MPTE in 1937,1 it has been described in several different adenocarcinomas. MPTE is characterised by highly progressive pulmonary symptoms in patients with a history of malignant disease, but it can also be the first clinical manifestation of an occult carcinoma. Due to limitations of diagnostic tests and its rapid progression, MPTE is often only diagnosed by autopsy.

We report two breast cancer patients who died of right heart failure caused by MPTE and provide a comprehensive review of the literature on MPTE in breast cancer patients. A PubMed search resulted in the identification of 15 patients, published in English or Dutch over the past 50 years, including those presented below (table 1). They show a wide variability in time span between cancer diagnosis and development of MPTE symptoms. MPTE should be treated immediately with anticancer therapy, in contrast to the administration of anticoagulants in case of pulmonary thromboembolism.
CASE DESCRIPTIONS

Case 1
A 69-year-old woman was admitted with rapidly progressive dyspnoea, weakness in her limbs and weight loss, 12 years after breast cancer diagnosis, pT1cN1M0, oestrogen receptor positive. Treatment consisted of an irradical lobectomy, followed by a mastectomy, adjuvant FEC chemotherapy (fluorouracil, epirubicin, cyclophosphamide), radiotherapy, and tamoxifen followed by letrozole. Since then, no evidence of recurrence was observed. We saw a pale woman experiencing shortness of breath, with a normal respiration rate, a saturation of 98% without oxygen suppletion, decreasing below 90% during exercise. No physical abnormalities were found. Routine laboratory analysis showed haemoglobin 6.4 mmol/l, certain symptoms.

Table 1. Case reports published in English or Dutch in the last 50 years regarding breast cancer patients diagnosed with MPTE

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Number of patients</th>
<th>Time since diagnosis primary cancer</th>
<th>First symptoms</th>
<th>Time to death since admission</th>
<th>Other metastatic sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>9 months</td>
<td>Dyspnoea on exertion, cough, flu-like syndrome, chest pain</td>
<td>Still alive after 17 months</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2 years / 12 years</td>
<td>Dyspnoea since a couple of weeks / pain in the abdomen</td>
<td>3 weeks / 10 days</td>
<td>Skeletal and bone marrow, Brain, ischaemia in ileum, kidney</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2 weeks</td>
<td>Two weeks of dyspnoea</td>
<td>Several days</td>
<td>Lung, liver, bone marrow</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>3 years</td>
<td>Dyspnoea</td>
<td>3 days</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>5 years</td>
<td>1 month of progressive cough and shortness of breath</td>
<td>7 days</td>
<td>Unknown</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Diagnosis after death</td>
<td>4 weeks of progressive dyspnoea, fatigue, low-grade fever</td>
<td>5 days</td>
<td>Liver</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1.5 years</td>
<td>5 days of dyspnoea and generalised weakness</td>
<td>Within one week</td>
<td>Bone, bone marrow and liver</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>Unknown</td>
<td>Unexplained dyspnoea</td>
<td>2-3 weeks after onset of dyspnoea</td>
<td>All 3 patients had diffuse metastatic spread, including bone marrow</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>9 months</td>
<td>Dyspnoea</td>
<td>3 weeks after onset dyspnoea</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>Unknown</td>
<td>Dyspnoea, weakness, anorexia</td>
<td>6 months after onset dyspnoea</td>
<td>All other organs</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>1 year / 12 years</td>
<td>Dyspnoea, muscle weakness, weight loss / dyspnoea and upper abdominal pain</td>
<td>12 days / 3 days</td>
<td>Bone and adrenal gland</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>15 months</td>
<td>Dyspnoea</td>
<td>1 year / 12 years</td>
<td>Liver</td>
</tr>
</tbody>
</table>

Current manuscript

2 | Still alive after 17 months | None |
4 | Skeletal and bone marrow, Brain, ischaemia in ileum, kidney |
5 | Lung, liver, bone marrow |
6 | Unknown |
7 | Unknown |
8 | Liver |
9 | Bone, bone marrow and liver |
10 | All 3 patients had diffuse metastatic spread, including bone marrow |
11 | Unknown |
12 | All other organs |

Current manuscript

2 | Bone and adrenal gland |


JANUARY 2014, VOL. 72, NO 1

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dyspnoea and abdominal pain in the right upper quadrant for one week. Liver enzymes were mildly elevated, lactate dehydrogenase was highly abnormal (2233 U/l; ULN 250 U/l), and cancer antigen 15-3 was elevated (98 E/ml). Three days after admission she developed respiratory failure and was admitted to the ICU. CTA imaging showed no pulmonary embolisms or other causes of pulmonary hypertension. An echocardiogram showed severe right heart failure. There was pulmonary hypertension, measured using a Swann-Ganz catheter. Blood tests showed a metabolic acidosis with high serum lactate (13.9 mmol/l), thrombocytopenia (platelets 42 x 10^9/l) and anaemia (haemoglobin 7.4 mmol/l). The condition of the patient did not warrant cytotoxic treatment. Despite maximal treatment she died of respiratory and haemodynamic failure. Autopsy revealed multiple microscopically small intravascular carcinomatous embolisms in the small arterioles of the pulmonary vasculature and in the sinusoids of the liver. In the right ventricle no signs of chronic failure or cardiomyopathy were detected, corresponding to the sudden onset. The presumed cause of death was right ventricular failure due to extensive pulmonary tumour emboli. The high serum lactate was probably due to circulatory failure resulting in anaerobic metabolism in the peripheral tissue. The low platelet count may be explained by the massive emboli resulting in high platelet use or by diffuse intravascular coagulation but other parameters necessary for this diagnosis, such as fibrogen and fragmentocytes, were not tested.

DISCUSSION

One of the first signs of MPTE is unexplained dyspnoea, with a rapidly progressive course within days or weeks. Differential diagnostics include lymphangitic carcinomatosis, vascular compression by a tumour, pulmonary thromboembolisms, pneumonia, pleural effusion, pericardial effusion, and heart failure e.g. chemotherapy-induced cardiotoxicity. Although only occasionally reported in literature, MPTE is thought to be underreported. An autopsy study of breast cancer patients reported that pulmonary tumour embolisation was the primary cause of death in four out of 100 patients reviewed.4 Reasons for missing the diagnosis of MPTE are lack of a sensitive test, as it cannot be found with CTA imaging or with laboratory analysis. MPTE should be considered after excluding the more common diagnoses, of which the most important is pulmonary embolism. The definite diagnosis can only be made by tissue examination. In patients with symptoms suggestive of MPTE in which no other diagnosis is made and with a (history of) malignancy, obtaining tissue, for example by means of transbronchial fine needle aspiration should be considered for the definite diagnosis. If untreated, MPTE may lead to the occlusion of peripheral pulmonary vasculature causing pulmonary hypertension with subsequent right ventricular failure and ultimately cardiovascular collapse. Although often fatal, survival of a breast cancer patient with MPTE treated with effective chemotherapeutics has been reported,7 proving that adequate treatment can be lifesaving. The treatment of choice is a cytotoxic regimen directed against the primary tumour, in this case breast cancer. MPTE can present as a manifestation of massive metastatic disease, but also as the only site involved. The aggressive nature does not leave much time for diagnostics, but if until recently the patient had a good performance status, limited disease localisation, and relevant systemic treatment options are available, the urgent initiation of systemic treatment should certainly be considered. Table 1 summarises the currently available descriptions of patients with MPTE. Although it may be the first presentation of cancer, most patients have been treated for breast cancer years before developing MPTE. As discrimination between MPTE and pulmonary thromboembolisms is difficult, the diagnosis often remains unclear and instead of treating the underlying malignancy, anticoagulation for suspected thromboembolism is given, which is ineffective. Autopsy, if performed, then reveals the MPTE.

CONCLUSION

MPTE is a rare insidious syndrome presenting with progressive dyspnoea and pulmonary hypertension in patients with widespread incurable cancer, a history of malignant disease or occasionally as the first symptom of occult malignancy, often breast cancer. Despite papers reporting high prevalence in autopsy series, MPTE is still highly unrecognised due to its difficulty to diagnose. The clinical diagnosis can be made in patients with dyspnoea for which no explanation is found on CTA and after cardiac evaluation and with other signs or symptoms of metastatic disease. Awareness of possible MPTE is of high importance as, if clinically possible, it is essential to initiate immediate cytotoxic treatment as this is the only possible treatment of this often fatal syndrome.

REFERENCES


11. Durham JR, Ashley PF, Dorencamp D. Cor pulmonale due to tumour emboli; review of literature and report of a case. JAMA. 1961;175:757-60.