GAVIN PUBLISHERS

Current Research in Complementary & Alternative Medicine

Samartzi V and Seront E. Curr Res Complement Altern Med: CRCAM-109.

DOI: 10.29011/CRCAM-109/100009

Case Report

From an Initial Diagnosis of Pulmonary Thromboembolic Disease to a Pulmonary Tumor Thrombotic Microangiopathy Consideration

Vassiliki Samartzi[1*], Emmanuel Seront[2]

[1]Department of Gynaecology, Hospital de Jolimont, Belgium

[2]Department of Medical Oncology, Hospital de Jolimont, Belgium

[*]**Corresponding author:** Vassiliki Samartzi, Department of Gynaecology, Hospital de Jolimont, Belgium. Tel: +3264234180; Email: vickysamartzi@yahoo.fr

Citation: Samartzi V, Seront E (2017) From an initial diagnosis of Pulmonary Thromboembolic Disease to a Pulmonary Tumor Thrombotic Microangiopathy consideration. Curr Res Complement Altern Med: CRCAM-109. DOI: 10.29011/CRCAM-109/100009

Received Date: 12 August, 2017; **Accepted Date:** 21 August, 2017; **Published Date:** 29 August, 2017

Abstract

Dyspnea is a common feature in cancer patients and causes are multiple. We describe a rapidly progressive dyspnea appearing in a woman with metastatic triple-negative breast cancer treated with the anti-angiogenic agent bevacizumab.

Clinical manifestations, biological findings and radiological features suggested initially thrombo-embolic disease, as anti-angiogenic agents such as bevacizumab are known to increase thrombotic events; anticoagulation was rapidly started with a close monitoring of anti-Xa activity. Respiratory symptoms, however, increased progressively over following days. In front of the absence of clinical improvement, we decided to perform lung biopsy but the rapid deterioration of this approach rendered this diagnostic approach unfeasible and the patient died rapidly.

Despite the absence of histological findings, Pulmonary Tumor Thrombotic Microangiopathy (PTTM) should be strongly considered in this patient. PTTM is usually misdiagnosed as thromboembolism disease, due to the poor knowledge of this entity. This case highlights the importance to consider this diagnosis early as natural progression is rapidly fatal and often impairs realization of diagnostic work-up.

Introduction

Dyspnea is a common feature in cancer patients and causes are multiple; dyspnea could be directly related to cancer progression (Pleuro-Pericardial Effusion, Lymphangitiscarcinomatosis, mediastinal involvement etc..) but can also be related to anticancer agent toxicity. Particularly, the new anticancer drugs such as targeted agents or immunotherapy can induce atypical respiratory disorders such as thromboembolism, cardiopathy, pneumonitis, Antiangiogenic agents such as bevacizumabare frequently used in different cancers including metastatic breast cancer and are known to increase the risk of thrombo embolic events through their action on angiogenesis [1]. Differential diagnosis should also include other potential less common causes. Pulmonary Tumor Thrombotic Microangiopathy (PTTM) is a clinical entity characterized by release of tumor cells in pulmonary circulation; these cells occlude small arteries and activate the coagulation system and release inflammatory mediators resulting in diffuse microangiopathy [2,3]. PTTM is unfortunately underestimated in cancer patients and is often misdiagnosed as pulmonary embolism as these two entities are both clinically undistinguishable. We report a case of severe and rapidly fatal pulmonary disorder occurring in a patient with metastatic breast cancer treated with bevacizumab. After an initial diagnosis of pulmonary embolism, PTTM diagnosis was considered but the rapid evolution impaired correct diagnostic work-up to confirm this entity, highlighting the importance of considering early this poorly known entity.

Case Report

A 48-year-old woman was diagnosed in august 2015 with bilateral voluminous breast tumors. Histology confirmed an invasive

ductal carcinoma with a triple negative pattern (Absence of Estrogen and Progesterone Receptor and Absence of Human Epidermal Receptor Growth Factor 2 (c-ErbB2 receptor)) and poor prognosis features including a high proliferative index (Ki67 100%) and peritumoral lymphatic vessels invasion. Tumors were associated with pathological lymph nodes bilaterally. Treatment included neo-adjuvant chemotherapy (four cycles of dose-dense anthracyclin-cyclophosphamide and 12 weekly cycles of Carboplatin-Paclitaxel Chemotherapy) followed by mastectomy and auxiliary dissection in June 2016. Radical surgery was mandatory because of radiotherapy unfeasibility due to a 26-year previous history of Hodgkin lymphoma that was treated by mantle field radiotherapy. This patient was then closely followed with a clinical examination and blood analysis every 3 months and a thoraces-abdominal CT every 6 months. Based on this work-up, there was no sign of cancer resurgence and this patient remained in complete remission till December 2017. At this time, she noticed apparition of multiple superficial red-violaceous nodules on right mastectomy area that clinically suggested Nodules de Velpeau (Figure 1). Biopsy of cutaneous nodules confirmed triple negative ductal carcinoma and peritumoral lymphatic invasion. Blood analysis was in normal range, including hemogram, electrolytes, liver and renal function. D-dimmers were also normal (0.5µg/ml). Tumoral marker CA 15.3 was importantly increased at 450 kU/L. Thoraco-abdominal CT showed multiple hepatic and bone metastatic lesions. Treatment with the cytotoxic agent paclitaxel and the anti-angiogenicbevacizumab was started rapidly (3weeks on/1week off corresponding to one cycle) and resulted after two cycles in number and size reduction of Nodules de Velpeau, decrease of CA 15.3 (220 kU/L) and radiological stability of metastatic lesions. Treatment was thus continued with the same drug regimen. However, after 2 further cycles, in april 2017, she was admitted in emergency for sub-acute breathlessness that appeared with exertion and that increased rapidly over one week to be present at rest. Dyspnea was associated with persistent dry cough and absence of pain. Pulmonary auscultation was strictly normal. Hemodynamic parameters revealed mild hypotension (100/60mmHg), tachycardia (120 bpm), tachypnea (20/min) and desaturation (89%) that normalized rapidly with oxygen therapy (2 liters/min).

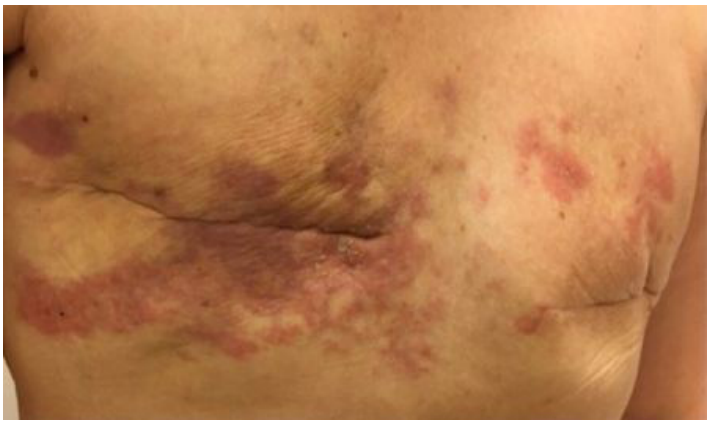

Figure 1: Superficial red-violaceous nodules on right mastectomy area suggesting Nodules de Velpeau.

In the laboratory work-up, there was no inflammatory syndrome (CRP 1mg/dl) and, compared to previous values, coagulation was strongly disturbed showing high level of D-Dimer (4.2 µg/ml). Blood gas analysis revealed hypoxemia (60 mmHg) andhypocapnia (28 mmHg). Thoracic CT was negative for pulmonary embolism and did not show any pleuro-pericardial effusion, infectious signs or lymphangitiscarcinomatosis. Interestingly, the main pulmonary artery was dilated, with a diameter (27.7mm) that was superior to aorta diameter (24.9mm), suggesting pulmonary hypertension (Figure 2).

Why D-Dimers were performed? They will be high in this patient any way due to the cancer.

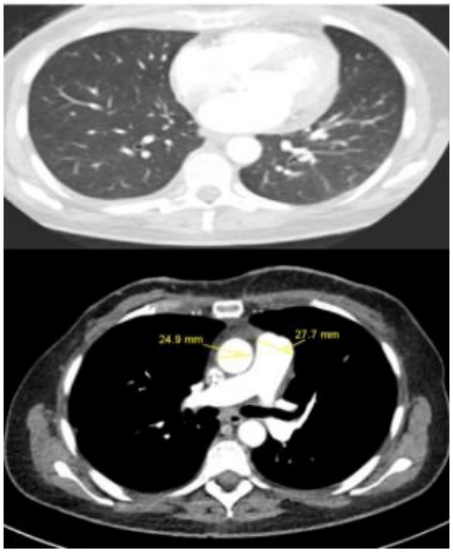

Figure 2: Thoracic CT negative for pulmonary embolism or active infection. Enlargement of the main pulmonary artery (27.7mm) compared to aorta (24.9mm) diameter suggesting pulmonary arterial hypertension.

Transthoracic echocardiogram confirmed pulmonary hypertension with an estimated pulmonary artery pressure of 60mmHg but a normal left ventricular systolic function (ejection fraction >60%). A pulmonary scintigraphy was rapidly performed and detected multiple bilateral sub-segmental defects on perfusion without ventilation anomalies (Figure 3). Abdominal CT and bilateral lower limb doppler showed no evidence of deep venous thrombosis; there was also no clinical evidence of upper limb thrombosis. Oncological work-up showed a stable disease; nodules deVelpeau were clinically stable and metastatic lesions were stable on imaging despite an important increase in CA 15.3 (800 kU/L) compared to previous value 2-month ago. All these features (Sub-Acute Dyspnea, Pulmonary Hypertension, D-Dimer increase and Context of Anti-Angiogenic Therapy) led us to consider a pulmonary peripheral thrombo-embolic disease, despite negative thoracic CT and absence of pelvic or inferior limb deep venous thrombosis.

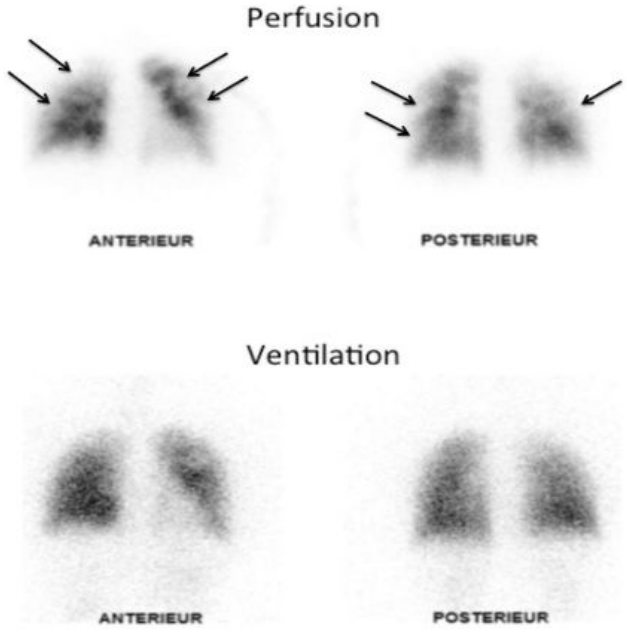

Figure 3: Pulmonary Scintigraphy detected multiple bilateral sub segmental defects on the perfusion without ventilation anomalies. Arrows show perfusion defect in peripheral sub-segmental arteries.

Low Weight Molecular Heparin (LWMH) was rapidly started at therapeutic doses with a close monitoring of anti-Xa activity. However, respiratory status did not improve in the following days and our patient required progressively increasing amount of oxygen. One week after HBPM initiation, a transthoracic lung biopsy as well as a Swan-Ganz catheterization with blood cytology analysis were planned but were rendered unfeasible due to the severe respiratory failure and the poor performance status of our patient. Our difficulties to get a diagnosis were clearly explained to our patient. She understood that the balance of benefit was outweighed by the risks and that a final diagnosis of PTTM could not help to improve her outcome. She asked herself palliative care and died few days later

Discussion

In this case report, we highlight the importance for a clinician to consider different potential hypothesis including less common disorders such as PTTM. The limitation of this case report is the absence of PTTM-proven histology due to a delay to consider this diagnosis and the unfeasibility to perform biopsy. The initial diagnosis was a thromboembolic disease in this patient. First, the initial clinical presentation (Brutal onset of dyspnea, hypoxemia and high D-Dimer levels) mimicked a pulmonary embolism. Secondly, our patient was treated with bevacizumab, an antiangiogenic agent that is known, through inhibition of angiogenesis and vascular homeostasis disturbance, to increase the risk of thrombotic events, with an incidence that rises up to 12 % in meta-analysis [1]. Third, despite negative thoracic CT, the multiple bilateral perfusion defects in the sub segmental pulmonary arteries observed in the pulmonary scintigraphy suggested pulmonary embolism. Finally, despite important tumoral marker ascension, cancer seemed controlled regarding clinical and radiological examination, impairing the hypothesis of a cancer-related pulmonary disorder. Therapeutic anticoagulation was thus started, but the progressive degradation of the respiratory function despite correct monitoring of anti-Xa activity led us to consider other potential hypothesis such as PTTM. A lung biopsy and/or a Swan Ganz catheterization with blood cytology was considered but these invasive techniques were rendered unfeasible due to the poor performance status of our patient who died rapidly. This case report highlights the importance to consider this diagnosis early in order to adapt the work-up rapidly in the disease course, before a rapid degradation of patient status.

PTTM syndrome is a rare entity that has been reported in 3% to 26% of autopsies conducted on patients with cancer. Accurate diagnosis of PTTM is rarely made ante-mortem and patients are often misdiagnosed of pulmonary thromboembolism[2]. PTTM is characterized by clusters of tumor cells in the pulmonary lymphovascular system that is not contiguous with metastatic foci. These cells not only mechanically obstruct the pulmonary vessels but also activate local and systemic coagulation that induces progressively a reactive concentric hypertrophy and intimal fibrosis of the vessels, resulting in fine in severe pulmonary hypertension and development of corpulmonale, as was the case in our patient [3,4].

The most common malignancies associated with development of tumor emboli are mucin-secreting adenocarcinomas originating in the breast, lung, stomach and colon [5]. It is also unknown whether some tumor characteristics could be associated with PTTM development. Our patient was initially treated for a triple-negative breast cancer, which is recognized as a highly angiogenic and angioinvasive disease, explaining the important peritumoral lymphatic vessels invasion observed on biopsies. It has been demonstrated that tumor cells localized in the pulmonary vessels, compared to primary tumor cells, are enriched in stem cell-like markers, reflecting an aggressiveness of these embolic cells [6]. The role of radiotherapy administered for Hodgkin lymphoma26 years ago in the development of a aggressive cancer remains unknown but radiotherapy is known to select aggressive tumor cells with high invasive properties [7]. Due to the low reported frequency of PTTM, it is currently unknown whether there is a relationship between the use of bevacizumab that could facilitate thrombotic mechanisms and PTTM.

Patients can present with a wide range of symptoms including dyspnea, chest pain and cough. These clinical manifestations are often indistinguishable from the more common thromboembolism. Due to the activation of coagulation cascade, laboratory analysis often shows consumptive coagulopathy with increased D-dimer level, as it was the case in our patient [2,4,5]. Thoracic CT is usually insensitive for tumor emboli due to the sub segmental localization of tumor cells clusters but can also show indirect signs of right heart overload, such as dilated and beaded peripheral pulmonary arteries. Further investigations should be performed and should include ventilation/perfusion pulmonary scintigraphy and echocardiography. Subtle abnormalities including sub segmental filling defect as seen in ventilation/perfusion scintigraphy are sometimes the only clues to the presence of tumor emboli, as observed in our patient [7]. Due to the increased resistance in the pulmonary vessels, echocardiography can demonstrate right-sided chamber enlargement and evidence of pulmonary hypertension. The “Gold Standard” for ante mortem diagnosis is either via open or video-assisted thoracoscopic lung biopsy [2-5]. Cytological examination of blood samples from a Swan-Ganz catheter has also been found feasible in the detection of tumor cells [8].

Treatments such as anticoagulation, thrombolysis, inferior vena, and cava filter placement seem to be ineffective in this disorder. Treatment of PTTM should be directed to the primary tumor. Even if some reports have shownthat early identification has led to better outcome with early treatment of cancer [9], prognosis is very poor; patients who present with signs and symptoms of subclinical corpulmonale often progress to death within days or weeks and the same had happened in the current case [10,11].

Many features suggest thus in this case report a PTTM diagnosis, including the clinical presentation that mimics thromboembolic disease, the negative CT scan that contrasts with positive pulmonary scintigraphy, the absence of improvement on therapeutic HBPM and the uncontrolled disease reflected by the tumoral marker increase. We do not know whether an earlier lung biopsy could have changed the outcome but it could have probably help our patient to understand her medical discomfort and to accept more easily the critical situation.

In conclusion, physicians should thus consider less common diagnosis such as PTTM in patients with aggressive tumor type and dyspnea and atypical pulmonary thromboembolic disease (Pulmonary Hypertension despite a negative thoracic CT scan, dis-

crepancy between thoracic CT and Pulmonary Scintigraphy, and no improvement despite a correct anticoagulation). Obtain a correct and early diagnosis by considering all hypotheses could in some cases help to improve patient out come but could also facilitates the patient understanding concerning their critical situation, particularly in oncology.

References

1. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S (2008) Risk of Venous Thromboembolism With the Angiogenesis Inhibitor Bevacizumab in Cancer Patients: A Meta-analysis. JAMA 300: 2277-2285.
2. Yao DX, Flieder DB, Hoda SA (2001) Pulmonary tumor thrombotic microangiopathy: An often missed antemortem diagnosis. Arch Pathol Lab Med 125: 304-305.
3. Pinckard JK, Wick MR (2000) Tumor-related thrombotic pulmonary microangiopathy: review of pathologic findings and pathophysiologic mechanisms. Ann Diagn Pathol 4: 154-157.
4. Von Herbay A, Illes A, Waldherr R, Otto HF (1990) Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension. Cancer 66: 587-592.
5. Roberts KE, Hamele-Bena D, Saqi A, Stein CA, Cole RP (2003) Pulmonary tumor embolism: a review of the literature. Am J Med 115: 228-232.
6. Kawasaki H, Ogura H, Arai Y, Baba S, Kosugi I, et al. (2010) Aggressive progression of breast cancer with microscopic pulmonary emboli possessing a stem cell-like phenotype independent of its origin. Pathology International 60: 228-234.
7. Broeks A, Braaf LM, Wessels LF, Vijvar De, Bruin De, et al. (2010) Radiation-Associated Breast Tumors Display a Distinct Gene Expression Profile. International journal of radiation oncology, biology, physics 76: 540-547.
8. Fink-Bennett D, Ravikrishnan KP, Underhill JA (1999) The checkerboard sign: a perfusion-ventilation pattern of pulmonary tumor microemboli. ClinNucl Med 24: 791-793.
9. Masson RG, Krikorian J, Lukl P, Evans GL, McGrath J (1989) Pulmonary microvascular cytology in the diagnosis of lymphangiticcarcinomatosis. N Engl J Med 321: 71-6.
10. Yang Y, Choi Y, Beom SH, Kim WJ, joen YK, et al. (2012) A Case Report of Breast Cancer with Extensive Pulmonary Lymphovascular Tumor Emboli.J Breast Cancer 15: 128-132.
11. Goldhaber SZ, Dricker E, Buring JE, Eberlein K, Godleski JJ, et al. (1987) Clinical suspicion of autopsy-proven thrombotic and tumor pulmonary embolism in cancer patients. Am Heart J 114:1432-1435.
12. Canova CR, Kuhn M, Allemann J (1998) Lethal pulmonary hypertension in a young woman caused by unrecognized haemangiosiscarcinomatosa. J Int Med 243: 255-257.