

## CASE REPORT

# An unexpected diagnosis in a patient with new-onset pulmonary infiltrates during adjuvant therapy for breast cancer

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## Abstract

The differential diagnosis of new-onset pulmonary infiltrates during adjuvant therapy in a cancer patient is challenging. Opportunistic infections, pulmonary drug-induced toxicity and metastatic dissemination of the underlying cancer are the most common causes. However, although infrequent, the development of a second primary pulmonary neoplasia should be taken into account. We present the clinical case of a breast cancer patient who developed progressive pulmonary infiltrates during adjuvant therapy, who was finally diagnosed as having a second lung neoplasm of unexpected histology.

## INTRODUCTION

The appearance of new-onset pulmonary infiltrates during adjuvant chemotherapy in a cancer patient represents a major challenge. The most frequent causes are opportunistic infections, pulmonary drug-induced toxicity and metastatic dissemination of the underlying cancer. In this context, suspicion about the development of a second primary pulmonary neoplasia, although infrequent, should be taken into account. We present the clinical case of a breast cancer patient who developed progressive pulmonary infiltrates during adjuvant therapy, who was finally diagnosed as having a second lung neoplasm of unexpected histology.

## CASE REPORT

A 55-year-old female patient presented in September 2016 with a 1-month history of persistent dry cough and asthenia while

on treatment with trastuzumab. Her past medical history was remarkable for a left breast cancer that was surgically removed 15 months before (ductal infiltrating carcinoma grade 2 pT1bN0snM0, estrogen receptor negative and human epidermal growth factor receptor 2 positive). She received radiotherapy and adjuvant chemotherapy, consisting in four cycles of fluorouracil, epirubicin and cyclophosphamide, followed by 8 weeks of paclitaxel combined with trastuzumab. After this, trastuzumab at standard dose of 6 mg/kg intravenously every 3 weeks was for a planned duration up to November 2016.

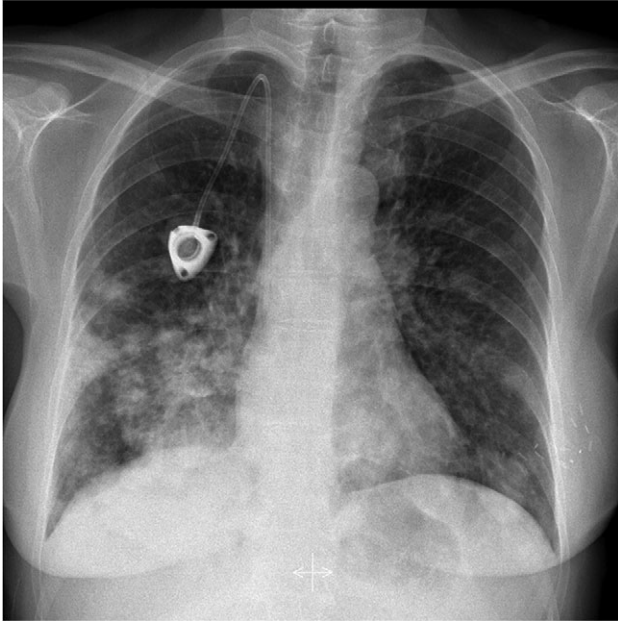
On examination, the patient was afebrile, and chest auscultation revealed fine crackles in the lower lobe of the right lung. She did not report fever, dyspnea or other complaints. Blood tests were normal except for a mild lymphopenia ( $0.7 \times 10^9$  cells/l, CD4 count 260 cells/mm<sup>3</sup>). A chest X-ray showed bilateral infiltrates, with micronodular pattern more prominent in

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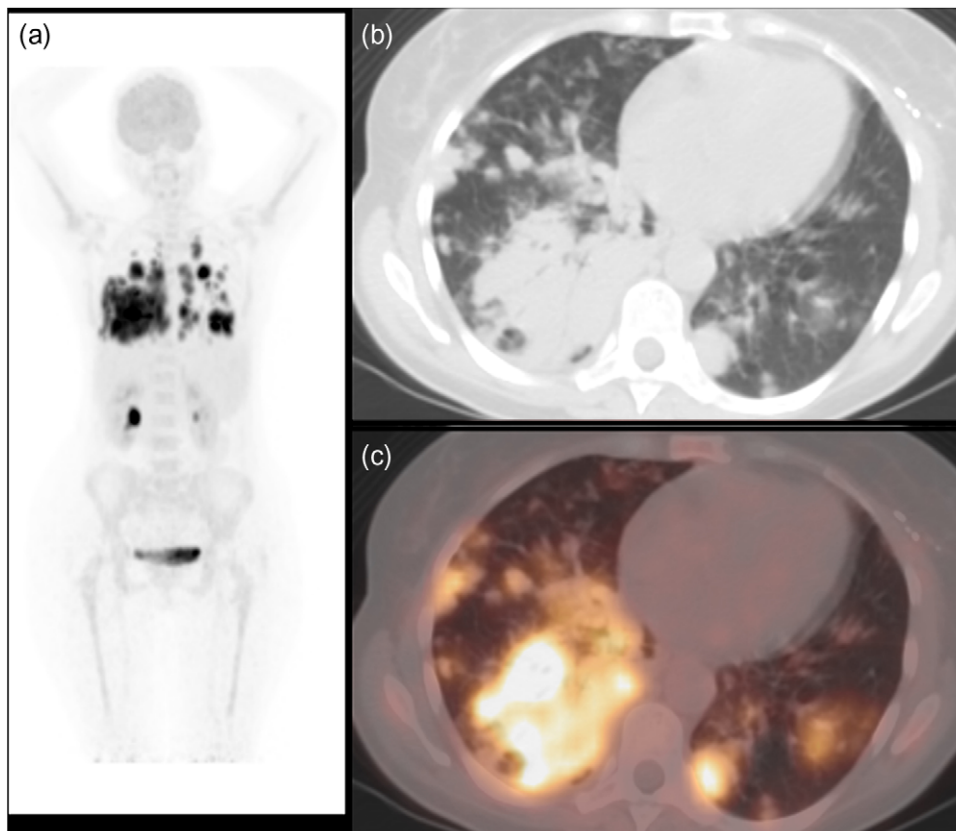
right lower lobe. A chest X-ray performed previous to breast cancer surgery was revised and found normal. A diagnosis of pulmonary toxicity from trastuzumab/organized pneumonia



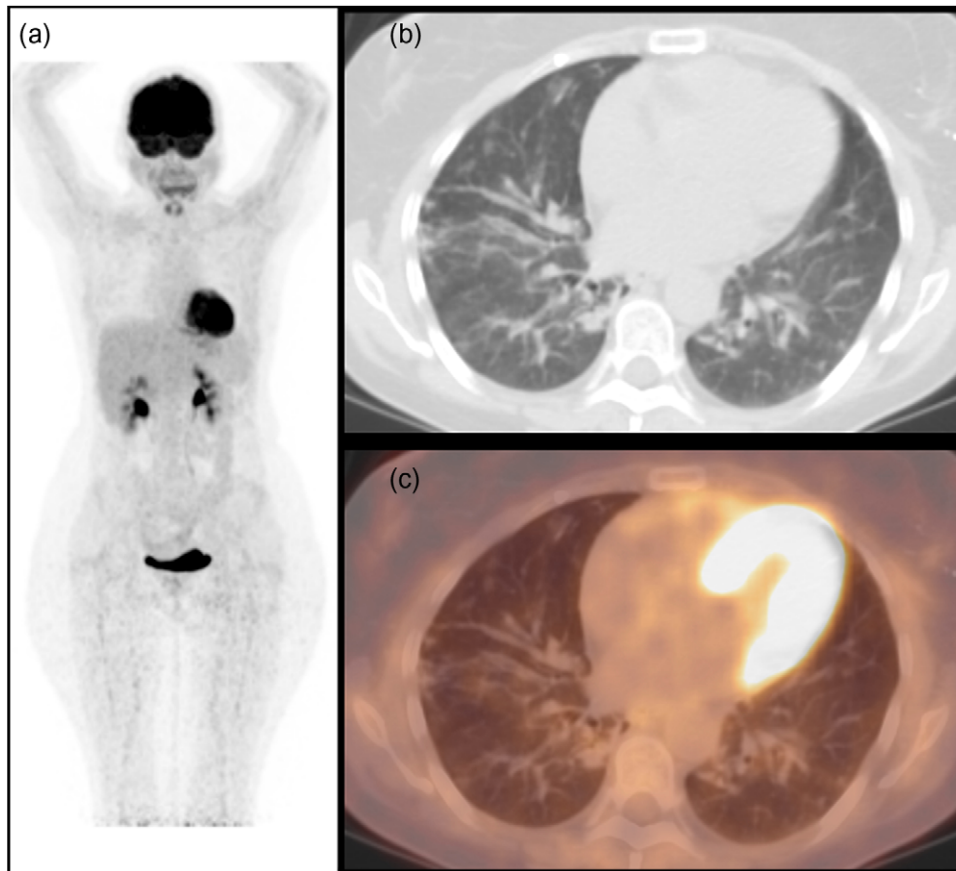
**Figure 1:** A chest X-ray following discontinuation of trastuzumab showed worsening of the patchy infiltrates, with alveolar condensations in the lower lung lobe, and bilateral lung nodules. A Port-a-Cath has been placed in the right infraclavicular region via the right subclavian vein.

was suspected, trastuzumab was discontinued, and a course of steroids, oral levofloxacin plus prophylaxis with trimethoprim-sulfamethoxazole was started. The patient did not improve right in the following 2 months, with persistent asthenia, cough and febricula, but no dyspnea. A new chest X-ray showed bilateral lung nodules, with patchy infiltrates and alveolar consolidations in the lower lung lobe (Fig. 1). A chest computed tomography (CT) scan showed multiple bilateral lung nodules with a confluent pattern in the lower lung lobe adopting an alveolar consolidation appearance, and some enlarged lymph nodes in the hilar and subcarinal regions. In view of those findings, a malignant process either metastatic or primary was suggested. <sup>18</sup>F fluoro-2-D-deoxyglucose (FDG) positron emission tomography-CT (PET/CT) scan showed an extensive bilateral pulmonary infiltration, more intense in the lower lung lobes, especially on the right side, with a maximum standardized uptake value of 25.5. No abnormal accumulation of the FDG was observed in either viscera or the lymph nodes (Fig. 2). Bronchoscopy was normal. Multiple samples from bronchoalveolar lavage (BLA) and trans-bronchial biopsies submitted for cytological and microbiological studies yielded negative results, including investigations for malignant cells, virus, fungus, bacteria, tuberculosis and pneumocystis.

An ultrasound-guided percutaneous biopsy of the lower lung lobe was performed. Microbiological investigations were again negative. Histology revealed a dense atypical infiltration of large cells, with negative immunohistochemical staining for cytokeratins (AE1/AE3, CK19), GATA3, sinaptophysin and TTF-1. Additional immunohistochemical staining showed CD20 (+), bcl6 (+), bcl2 (+), a high ki67 proliferation index; while CD10, CD3, and *in situ* hybridization for Epstein-Barr virus were negative. Bone marrow



**Figure 2:** <sup>18</sup>F-FDG-PET/CT before treatment: (a) MIP (maximum intensity projection). (b) Axial CT: multiple bilateral pulmonary nodules and areas of alveolar consolidation in right lower lobe. (c) Axial PET/CT: extensive and intense tracer uptake in both lungs.



**Figure 3:**  $^{18}\text{F}$ FDG-PET/CT end of treatment: (a) MIP (maximum intensity projection). (b) Axial CT: almost complete response (remaining small bilateral ground-glass opacities). (c) Axial PET/CT: complete metabolic response. Residual tracer uptake in both lungs. Bilateral basal infiltrates (some of them nodular) with very low uptake.

biopsy was normal. Based on those findings, a diagnosis of stage i.e. international prognostic index 1 (elevated serum lactate dehydrogenase), primary diffuse large B-cell lymphoma (DLBCL) of the lung was established.

The patient started chemotherapy with cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP) with rituximab with excellent tolerance and a quick resolution of previous symptoms. After completing six cycles, the chest CT-scan showed almost complete response with remaining small bilateral ground-glass opacities. The PET/CT showed a complete metabolic response with very low-residual tracer uptake in both lower lung lobes (Fig. 3).

## DISCUSSION

Primary pulmonary lymphoma (PPL) is a rare neoplasm that comprises 0.3% of all primary pulmonary malignancies, <1% of all lymphomas and 3–4% of all the extranodal lymphomas [1, 2]. Definition of PPL implies that lymphoma is confined to the lung (parenchyma and/or bronchi of one or both lungs), with or without hilar or mediastinal lymph nodes involvement at the time of diagnosis or during the following 3 months [3, 4]. The most frequent subtypes are extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma (70–90%), and DLBCL (5–20%) [4, 5]. The diagnosis of PPL may be elusive and thus, a high index of suspicion is needed. Radiological appearance shows isolated or multiple nodules in one or both lungs, and alveolar opacities, usually associated with an air bronchogram.

CT-scan reveals bilateral involvement in more than 70% of cases, and less frequently diffuse reticulonodular opacities, atelectasis, pleural effusion or hilar or mediastinal lymphadenopathy [1, 5, 6]. Bronchoscopy with biopsies and BAL provides cytological and histological samples for microbiology, immunohistochemistry, flow cytometry or molecular techniques. Image-guided percutaneous transparietal aspiration and biopsies may be useful especially for peripheral nodules or masses. Video-assisted thoracoscopic surgery or open lung biopsy may be needed especially in solitary lesions.

Treatment strategies for PPL are mainly based on the histological type and the extent of disease. Surgical resection is proposed, especially for localized resectable lesions. A complete resection with negative margins in 40% of cases and survival rates at 5 year and 10 years of 67% and 56%, respectively, have been reported [7]. For bilateral or extended disease, chemotherapy with protocols employed in nodal B-cell lymphomas are used, such as chlorambucil-rituximab for MALT lymphoma [8] and CHOP with or without rituximab for DLBCL [9, 10]. For the latter, a complete response rate in 83–94% and 5-year overall survival above 80% have been reported.

In conclusion, the presence of a pulmonary neoplasia (metastatic or primary as in our case) must be excluded in breast cancer patients with new-onset pulmonary infiltrates while receiving adjuvant therapy. Invasive techniques like bronchoscopy, imaging-guided percutaneous biopsy or even surgical biopsy may be needed to reach a final diagnosis. Although rare, PPL should be taken into account since it may be a potentially curable disease.

**CONFLICT OF INTEREST STATEMENT**

None declared.

**FUNDING**

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**CONSENT**

Consent for publication was obtained from the patient (Oxford University Press Patient Consent Form).

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