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CASE REPORT

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Bevacizumab-induced pulmonary cystic disease

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Abstract

The use of Bevacizumab has significantly advanced the treatment of various malignancies. Bevacizumab's inhibition of angiogenesis is a known mechanism that impedes tumour growth and facilitates chemotherapy delivery; however, its association with the development of cystic lung disease is not fully understood. We report a unique case of a 73-year-old woman with a past medical history of metastatic endometrial adenocarcinoma status post-chemotherapy with bevacizumab that presented with worsening respiratory symptoms. A follow-up chest CT scan post chemotherapy showed the transformation of the metastatic lesions into cystic formations. After further extensive evaluation, she was diagnosed with pulmonary cystic disease secondary to bevacizumab. This case illustrates a rare presentation of secondary pulmonary cystic disease following Bevacizumab therapy in a patient with metastatic endometrial adenocarcinoma. It highlights the importance of recognizing uncommon side effects of targeted immunotherapy and underscores the need for ongoing research to understand the underlying mechanisms and manage such complications effectively.

KEYWORDS

antiangiogenic, bevacizumab, cystic lung disease, metastatic endometrial adenocarcinoma

INTRODUCTION

The advent of targeted therapies in oncology, such as Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has revolutionized the treatment landscape for various malignancies. While these therapies have significantly improved patient outcomes, their unique adverse effect profiles present new clinical challenges. This case report highlights a rare and complex presentation of secondary pulmonary cystic disease in a patient with a metastatic endometrial adenocarcinoma, following treatment with Bevacizumab combined with carboplatin and paclitaxel. Through this case report, we will emphasize the potential pulmonary complications associated with Bevacizumab.

CASE REPORT

A 73-year-old female with a past medical history of left breast adenocarcinoma (2010) status post lumpectomy, chest radiation, and letrozole, and metastatic endometrial adenocarcinoma (2017) status post total hysterectomy, bilateral salpingo-oophorectomy, pelvic radiation, and five cycles of chemotherapy regimen with carboplatin, paclitaxel, and bevacizumab presented to the pulmonary clinic for evaluation of cystic lung disease.

Three years prior to presentation, she was diagnosed with endometrial adenocarcinoma. She received definitive treatment with a total hysterectomy, bilateral salpingo-oophorectomy, and pelvic radiation, A CT scan of the chest at this time revealed a single nodular opacity in the right lower lobe, prompting a recommendation for follow-up CT imaging for monitoring. However, 2 months later, she developed symptoms including exertional dyspnea, cough, and blood-tinged sputum. A repeat CT chest demonstrated numerous solid masses and nodules of variable size and shape throughout both lungs, with the largest lobulated mass in the right lower lobe measuring 4.9 × 3.8 cm. These findings suggested a radiological appearance consistent with metastatic disease. A CT-guided biopsy of a lesion in the left upper lung lobe confirmed metastatic endometrial

adenocarcinoma. Subsequently, the patient commenced a chemotherapy regimen with carboplatin, paclitaxel, and bevacizumab, completing a total of five cycles. Follow-up CT chest imaging after completion of chemotherapy showed the transformation of the solid nodular and mass-like lesions into cystic formations, correlating with the sites of previous metastases. Serial CT scans over the next couple of years demonstrated complete resolution of her metastatic disease and stabilization of the cystic lung disease, with the cysts anatomically corresponding to the previously identified metastatic sites (Figure 1). She was referred to the pulmonary clinic for further evaluation.

Extensive workup, including serum free light chain, protein electrophoresis, immunofixation, alpha-1 antitrypsin enzyme level and genotype, and a broad range of rheumatological serology tests, returned negative results. A follow-up PET scan at this time showed no active uptake (Figure 2), and a transbronchial biopsy excluded the presence of

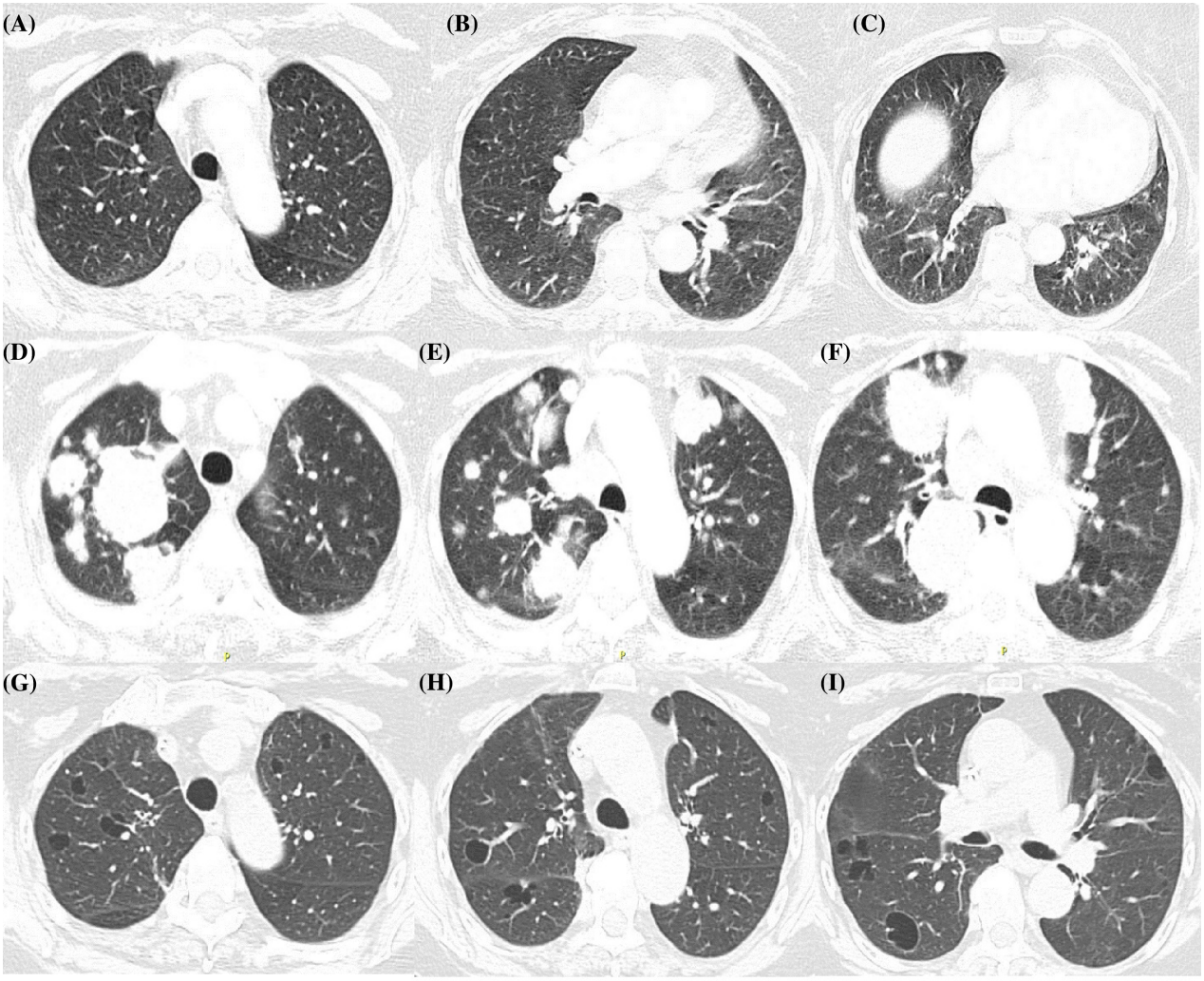

FIGURE 1 (A) CT chest of the upper lung field shows normal parenchyma with no metastatic or cystic lung disease appreciated. (B) CT chest of the mid lung field shows normal parenchyma with no metastatic or cystic lung disease appreciated. (C) CT chest of the lower lung field showing subpleural solitary nodular opacity of the right lower lobe (metastatic endometrial carcinoma). No pulmonary cysts, or any other pathological findings noted. (D) CT chest of the upper lung field shows numerous solid masses and nodules throughout both lungs of variable size and shape and random distribution, conglomerate mass in the right apex. (E) CT chest of the upper lung field shows numerous solid masses and nodules throughout both lungs of variable size and shape and random distribution. (F) CT chest of the upper lung field and the superior segments of lower lobes bilateral shows a few solid masses and nodules throughout both lungs of variable size and shape and random distribution. The right lower lobe superior segment mass measuring 4.9 × 3.8 cm (red arrow). (G) CT chest of the upper lung field, status post treatment with Taxol based chemotherapy and Bevacizumab. shows resolution of pulmonary metastasis and bilateral asymmetrical cystic lung disease, of variable size, shape, air filled, with well-defined thin walls, anatomically related to a previously noted endometrial metastatic lesions. (H) CT chest of the upper and lower lung field, status post treatment with Taxol based chemotherapy and Bevacizumab, shows resolution of pulmonary metastasis and a new onset bilateral asymmetrical cystic lung disease, of variable size, shape, air filled, with well-defined thin walls, anatomically related to a previously noted endometrial metastatic lesions. (I) CT chest of the right middle lobe, lingula along with partial upper and lower lobes, status post treatment with Taxol based chemotherapy and Bevacizumab. shows resolution of pulmonary metastasis and a new onset bilateral asymmetrical cystic lung disease, of variable size, shape, air filled, with well-defined thin walls, anatomically related to a previously noted endometrial metastatic lesions.

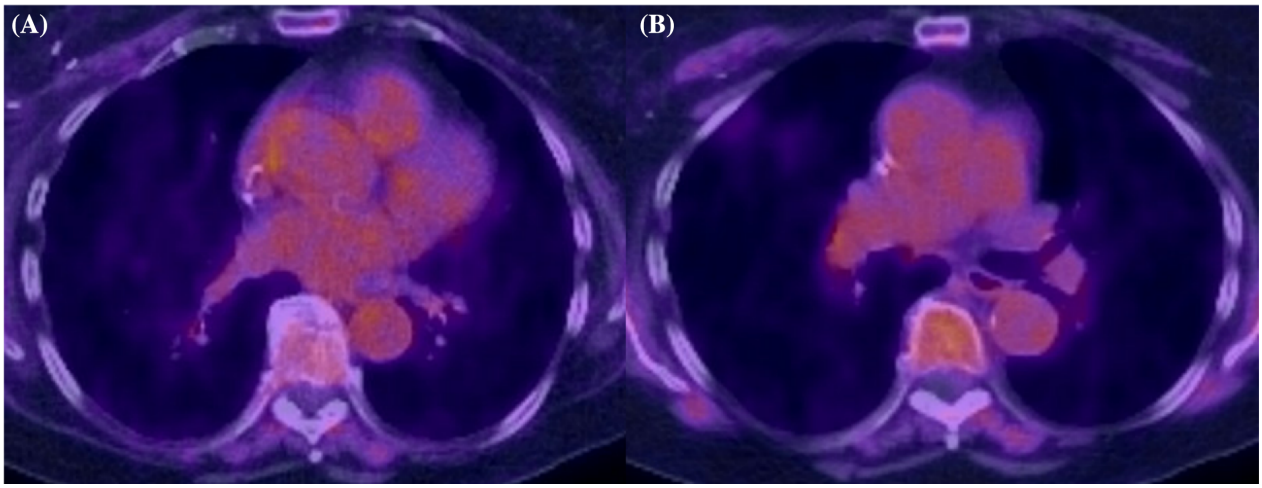

FIGURE 2 (A) PET CT scan performed 3 years after chemotherapy with Bevacizumab shows no FDG uptake of her pulmonary cystic disease, moreover no FDG uptake of mediastinal or hilar lymph nodes. (B) PET CT scan shows no FDG uptake of her pulmonary cystic disease, moreover no FDG uptake of mediastinal or hilar lymph nodes.

metastatic cystic endometrial adenocarcinoma. Additionally, the patient was evaluated for a range of differential diagnoses, including lymphangioleiomyomatosis (LAM), amyloid disease, light chain deposition disease, lymphocytic interstitial pneumonia (LIP), pulmonary Langerhans cell histiocytosis (PLCH), and syndromes such as Birt-Hogg-Dube, neurofibromatosis, Marfan, and Ehlers-Danlos. However, clinical signs and further investigations, including further staining of the biopsy with HMB-45, a monoclonal antibody that reacts with an antigen in melanocytic tumours, and whole genome sequencing (TSC1, TSC2, FLCN, FBN1, NF1, COL5A1, and COL5A2) did not support these diagnoses.

The patient was diagnosed with secondary pulmonary cystic disease, related to her Bevacizumab therapy. Over the next 2 years, she demonstrated stable cystic lung disease without changes in the number, size, or morphology of the cysts, no recurrence of neoplasm, and maintained functional capacity. Pulmonary function tests revealed normal spirometry and a mildly reduced diffusion capacity of carbon monoxide at 52% predicted.

DISCUSSION

Bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), inhibits neovascularization by binding to VEGF-A isoforms and preventing their interaction with VEGFR-1 and VEGFR-2 receptors on endothelial cells. This mechanism not only impedes vessel growth but also facilitates chemotherapy delivery through vascular normalization.[1,2] It was the first anti-angiogenic treatment approved by the Food and Drug Administration. Initially, it gained approval for use in combination with chemotherapy for metastatic colon cancer. Subsequently, it received approval for other tumour types, including kidney, cervical, ovarian, lung cancer, and recurrent glioblastoma multiforme.[3]

In advanced and recurrent endometrial carcinoma, Paclitaxel and carboplatin constitute the standard chemotherapy.[4] Bevacizumab has shown promise in this context, with studies indicating improved efficacy when combined with chemotherapy, as per Chen et al.'s 2021 systematic review and meta-analysis.[5] However, Bevacizumab's adverse effects range from haematological complications (anaemia, leukopenia, neutropenia, thrombocytopenia) to hypertension, thromboembolic events, and even central nervous system haemorrhage.[5] Of particular interest in this case is the development of cystic lung disease following Bevacizumab treatment, a relatively under-explored area in literature.

Cystic lung diseases, identified by the presence of lung parenchyma cysts on high-resolution computed tomography scans, stem from various etiologies, including neoplastic, congenital, lymphoproliferative, and infectious causes. Distinguishing these from emphysema, α1-antitrypsin deficiency, and late-stage interstitial lung diseases is crucial for accurate diagnosis.[6,7] The development of lung cysts and cavities following Bevacizumab treatment, as documented by Patel et al., is an intriguing phenomenon. This occurrence may be attributed to the inhibition of tumour-associated angiogenesis, leading to central tumour necrosis and consequent transformation of neoplastic pulmonary nodules into cystic lesions. The pathophysiology behind such transformations is not fully understood but could involve a range of mechanisms, including ischemia, bronchial obstruction, lung parenchymal remodelling, or a combination of these factors.[8,9] Tumour cavitation has been observed in patients treated with other antiangiogenic drugs, such as Endostar, a recombinant human endostatin, and chemotherapy agents like Docetaxel from the taxane family. These cases suggest a potential link between antiangiogenic treatment and the development of lung cancer cavitations which may correlate with a more favourable prognosis.[10]

In conclusion, while Bevacizumab and similar antiangiogenic agents offer significant benefits in cancer therapy, awareness of their less common side effects, such as cystic lung disease, is essential for optimizing patient outcomes. This case adds valuable insight to the literature and underscores the necessity for further research to elucidate the mechanisms underlying the development of cystic lung disease post-Bevacizumab treatment.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing and editing of this manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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