Case Report

Trastuzumab-induced pulmonaryfibrosis: A case report and review of literature

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ABSTRACT

Optimal treatment for human epidermal growth factor receptor 2 (HER2)/neu-positive, node-positive early breast cancer should include the monoclonal antibody trastuzumab. This relatively new targeted agent has shown very limited pulmonary toxicity. We report a case of Trastuzumab-induced pulmonary fibrosis in a 41-year-old female that occurred 4 months after starting adjuvant trastuzumab. To the best of our knowledge, this is the first ever report of trastuzumab-induced pulmonary fibrosis in the world of medical literature.

Key words: Breast cancer,pulmonary fibrosis, trastuzumab

INTRODUCTION

The human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20-25% of human breast cancers and is an independent adverse prognostic factor. Trastuzumab is a humanized monoclonal antibody that selectively binds to the extracellular domain of the HER2/neu growth factor receptor. It is indicated for the treatment of metastatic breast cancer with overexpression of HER2 protein, as well as for the adjuvant therapy of node-positive, HER2/neu overexpressing breast cancer along with other chemotherapeutic drugs. While cardiotoxicity of trastuzumab is well recognized, particularly when it is used in combination with anthracyclins, unusual pulmonary toxicities are now becoming apparent.

CASE REPORT

A 41-year-old female, who was a diagnosed case of carcinoma of right breast and had already undergone modified radical mastectomy and axillary dissection, was referred to our department for adjuvant chemoradiation. She had a pT3N1M0, grade III, ER-negative/PR-negative/HER2/neu-positive, intraductal carcinoma. After receiving four cycles of AC chemotherapy (doxorubicin 60 mg/m^2 iv on day 1, cyclophosphamide 600 mg/m^2 iv on day 1, every 2 weekly), she was given adjuvant external beam radiation (50 Gy/25fr) to right chest wall and supraclavicular fossa. She tolerated radiation well, and 2 weeks after completion of radiotherapy, paclitaxel chemotherapy (175 mg/m^2 iv on day 1, every 3 weekly forfour cycles) was started. Due to some logistic and economic issues, she could not afford trastuzumab along with paclitaxel, and the first cycle of trastuzumab (8 mg/kg iv on day 1) was given 2 weeks after the last dose of paclitaxel. After that she received five more cycles of trastuzumab (6 mg/kg iv, every 3 weekly). One week after the sixth cycle of trastuzumab, she presented with complaints of dyspnea and dry cough. On clinical examination, she was afebrile with increased respiratory rate (28/minute). Bilateral wheezing was present on chest auscultation. Her SpO_2 was 87% on room air. Chest X-ray showed ground-glass opacification of the lungs. Routine hematological and biochemical parameters were within normal range, echocardiography was normal. Spirometry yielded the following results: forced expiratory volume in 1 second (FEV1) 48.7% and forced vital capacity (FVC) 42.7%. After admission, she was treated with moist O_2 inhalation (4 liters/hour), intravenous antibiotics and bronchodilators in propped up position. Spiral computed tomography (CT) thorax showed diffuse extensive ground glass attenuation, which was more prominent in the

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subpleural region, intermixed with interlobular septal thickenings, without any pleuro-pericardial effusion. These findings were suggestive of diffuse alveolar damage or acute phases of interstitial lung disease [Figure 1]. Bronchoscopic lung biopsy revealed interstitial widening with moderate interstitial chronic inflammatory infiltrate composed of lymphocytes and histiocytes along with intraalveolar fibroblastic plugs [Figure 2]. Both blood and urine cultures were negative. As no other underlying cause of dyspnea could be identified, the patient was diagnosed as a case of trastuzumab-induced interstitial fibrosis. Antibiotics were withdrawn and prednisone 40 mg orally once daily was started. After 2 weeks of steroid therapy, her symptoms improved a lot and she was discharged without any need for O_2 inhalation, with gradual tapering dose of prednisolone over 4 weeks. No more cycle of trastuzumab was given thereafter.

DISCUSSION

Trastuzumab has become the standard of care in the management of (HER2)-over expressing breast cancers, both in the metastatic and adjuvant setting. Emerging data has shown continued efficacy of the drug even after disease progression in combination with chemotherapy.

Trastuzumab has been well tolerated in several series, and its addition to chemotherapy does not significantly increase the frequency of side effects.[1] The incidence of trastuzumab-induced pneumonitis is 0.4-0.6%, with 0.1% mortality. Trastuzumab-induced pneumonitis may present with rapidly progressive pulmonary infiltrates and respiratory failure after receiving 1 dose of trastuzumab or after 6 weeks of therapy.[2,3] Acute neutrophilicalveolitis and organizing pneumonia after trastuzumab treatment also have been reported.[4] Infusion-related events, including hypotension, angioedema, bronchospasm, dyspnea, fever, chills, and urticaria has been reported to occur in about 15% of patients. But they are rarely severe, and more common during the first administration of the drug.[5-7] In a retrospective analysis of the safety of herceptin immunotherapy in metastatic breast cancer, trastuzumab was administered to 25,000 patients, and the only respiratory-associated serious adverse event was infusion-related bronchospasm, which usually occurred within 2.5 h of administration.[8] Severe episodes of hypotension, bronchospasm, and hypoxemia leading to death are rare.[9]

Paclitaxel is also known to cause pneumonitis with estimated frequencies of 0.73-12%. Dyspnea, cough, hypoxemia, and pulmonary infiltrates usually develop 1 week to 3 months after treatment.[10-12] Hypersensitivity reactions are well-recognized complications ofpaclitaxel therapy and typically occur with the first or second dose.[10]

Our patient's symptoms appeared much later than what has been reported in the literature for trastuzumab and paclitaxel separately. Although there is no clear diagnostic test to confirm the actual offensive drug of pulmonary fibrosis in this case, but in view of the fact that the patient became symptomatic during trastuzumabmonotherapy, 4 months after starting therapy, trastuzumab might be the probable cause of lung injury in this patient.

CONCLUSION

We report an extremely rare case of trastuzumab-induced pulmonary fibrosis in a 41-year-old female that occurred 4 months after starting adjuvant trastuzumab. To the best of our knowledge, this is the first ever report of trastuzumab-induced pulmonary fibrosis in the world of medical literature. Although pulmonary toxicity is unusual with

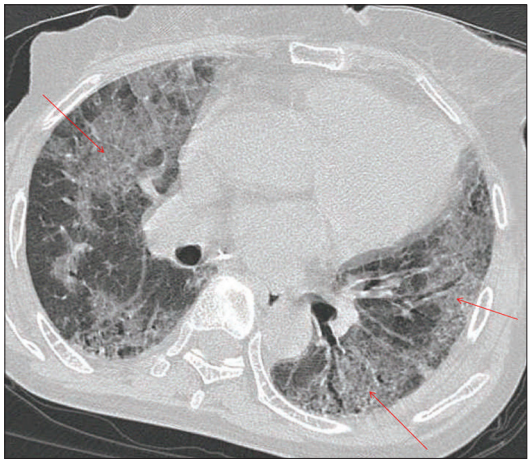

Figure 1: HR-CT thorax showing diffuse extensive ground glass attenuation, intermixed with interlobular septalthickenings, suggesting diffuse alveolar damage

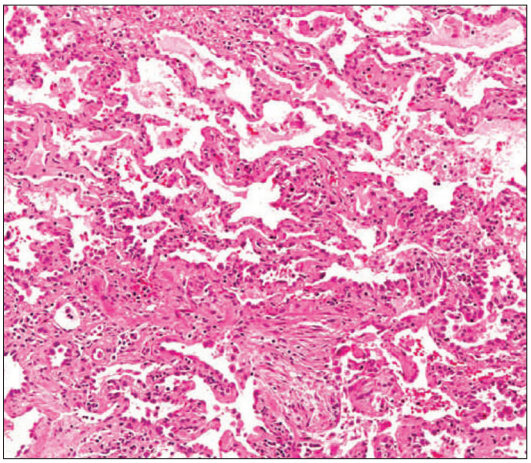

Figure 2: Photomicrograph of bronchoscopic lung biopsy showing interstitial widening with moderate interstitial chronic inflammatory infiltrate composed of lymphocytes and histiocytes along with intraalveolar fibroblastic plugs (H and E, ×100)

trastuzumab administration, and pulmonary fibrosis is rarer, it is important to be aware of this specific toxicity. Moreover, early recognition andappropriate treatment are of utmost importance to prevent potentially fatal sequelaeof this condition.

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