Case Report

An unusual flare of anti-synthetase syndrome during concurrent trastuzumab therapy given for recurrent breast cancer

Timothy D. Reynolds¹, Vivek Mohan², Matthew Roy³, Nathan Manghat⁴, Huzaifa Adamali⁵, Harsha Gunawardena⁶

Abstract

We present the case of a patient with relapsing anti-synthetase syndrome (ASS) that may have been triggered by monoclonal antibody trastuzumab therapy given for breast cancer. A 52-year-old female with a history of anti-Jo1-associated ASS went into remission with glucocorticoids and mycophenolate mofetil. Her past history included invasive ductal carcinoma of the right breast that was fully treated six years prior to the onset of ASS. She subsequently developed recurrent right-sided breast cancer that was treated with right mastectomy and six cycles of cyclophosphamide-docetaxel chemotherapy. She commenced adjuvant trastuzumab and letrozole therapy, and following the sixth injection of trastuzumab, she was admitted with clinical features consistent with a flare of ASS, which included swinging fever, interstitial lung disease, myositis, and possible subclinical myocarditis, despite recent treatment with cyclophosphamide. She responded to intravenous IV methylprednisolone followed by increased doses of oral glucocorticoids, and she remains stable on immunomodulatory treatment and letrozole monotherapy given for breast cancer. This report provides a concise overview of ASS along with other cases of cardiac and pulmonary diseases attributed to trastuzumab therapy reported in the medical literature.

Keywords: Drug-induced rheumatic disease, myositis and muscle disease, neoplasia, respiratory, cardiovascular

Introduction

Anti-synthetase syndrome (ASS) is an autoimmune connective tissue disease (CTD) defined by the presence of anti-aminoacyl tRNA synthetase (anti-ARS) autoantibodies. Recently, this condition has been recognized as a discrete entity within the spectrum of what has been traditionally known as polymyositis and dermatomyositis. Currently, there are eight identified anti-ARS autoantibodies, with anti-Jo1 being the most frequently observed. The characteristic clinical features of ASS include myositis, inflammatory arthropathy, skin lesions, constitutional symptoms including fever, and interstitial lung disease (ILD) (1). ASS is a spectrum disorder where patients sometimes present with limited manifestations such as ILD and fever. Myocardial involvement is rare, and unlike other dermatomyositis serological phenotypes (particularly anti-TIF1 or anti-NXP2 subsets), cancer-associated myositis in ASS is less common (1). Here we present the case of a patient with relapsing ASS that may have been triggered by the concurrent use of monoclonal antibody trastuzumab therapy administered alongside chemotherapy for recurrent breast cancer.

Case Presentation

A 52-year-old Afro-Caribbean female with a three-year history of anti-Jo1-associated ASS presented with proximal weakness, elevated creatine kinase levels (4470 IU/L), and non-specific interstitial pneumonia (NSIP) and organizing pneumonia (OP) patterns on performing high-resolution computed tomography (HRCT) imaging. Her past medical history included invasive ductal carcinoma of the right breast that was diagnosed and fully treated six years prior to the presentation of ASS. Myositis and ILD responded well to reducing doses of oral glucocorticoids and mycophenolate mofetil; she showed significant clinical improvement, normalization of creatine kinase levels, and improvement in lung physiology. Seven years after her original breast cancer and one year after ASS remission, she developed recurrent right-breast invasive ductal carcinoma. She remained on low-dose glucocorticoids, and mycophenolate mofetil was stopped prior to undergoing right-sided mastectomy. Following surgery, she was treated with six cycles of cyclophosphamide (600 mg/m²) and docetaxel (75 mg/m²). Following the initial chemotherapy regimen, she remained stable with no flare of CTD features. During her chemotherapy regimen, she underwent adjuvant therapy with three weekly subcutaneous trastuzumab injections and hormonal treatment with letrozole. She was admitted with worsening breathlessness, swinging fever and leukopenia following...
the sixth course of chemotherapy and sixth dose of trastuzumab. Her clinical examination and plain chest radiographs demonstrated bilateral chest consolidation with pleural effusions. She was initially treated for presumed neutropenic sepsis with intravenous antibiotics and granulocyte colony-stimulating factor. Despite these treatments, there was further deterioration in her clinical and physiological respiratory function (forced vital capacity was 69% of the predicted level; transfer factor for carbon monoxide was 33% of the predicted level with desaturation on exertion). She also described recurrence of proximal lower limb myalgia accompanied by an increase in creatine kinase levels to 3390 IU/L and troponin-T levels to 112 ng/L (normal level: <14 ng/L). HRCT imaging demonstrated a marked peri-bronchocentric patchy consolidation and subpleural reticulation, consistent with NSIP/OP patterns (Figure 1). The combined features, which included swinging fever, ILD, myositis, and possible subclinical myocarditis, represented a flare of ASS. She responded well to IV methylprednisolone; an increased dose of oral glucocorticoids and mycophenolate mofetil was restarted. Echocardiography along with a cardiac MRI scan demonstrated long-axis LV systolic impairment and regional hypokinesia but not myocardial edema, although the MRI scan was performed after steroids were started, so this may have masked some features. There was a marked overall clinical improvement alongside the improvement in lung physiology and normalization of creatine kinase levels (Figure 2). The patient remains stable on immunomodulatory treatment along with letrozole monotherapy for breast cancer.

Written informed consent was obtained from the patient.

Discussion

Trastuzumab is a monoclonal antibody to the human epidermal growth factor 2 (HER-2) receptor. It is known to significantly reduce the rate of breast cancer recurrence, but it has been linked to cardiac toxicity, particularly when used in conjunction with anthracycline chemotherapy (not in our patient) (2). Our patient was treated with 14 cycles of trastuzumab therapy as part of her treatment regimen when she first developed breast cancer six years prior to presentation; however, it was stopped following a small asymptomatic drop in her left ventricular ejection fraction from 63% to 50%. Her cardiac function had recovered prior to commencing treatment for recurrent breast cancer, so the decision was made to include trastuzumab as part of her treatment regimen, along with performing repeat echocardiography at three-month intervals to monitor deterioration. Trastuzumab has also been linked to precipitating ILD (3). This can have various acute manifestations including infusion reactions, acute lung injury, or pneumonitis among patients who have recently started taking the medication. There have also been reports of delayed onset of OP in patients taking trastuzumab for prolonged periods (3-5).

We believe that this is the first recorded case of a flare of ASS temporally linked to the com-
mencement of trastuzumab therapy, with marked deterioration of ILD, swinging fever, myositis, and possible myocardial involvement. While it is possible that the flare of the disease can be partially explained by the patient having stopped taking mycophenolate mofetil at the time of commencing chemotherapy, our case is noteworthy as the patient received cyclophosphamide pulses as part of the breast cancer therapy, which is a recognized treatment option for ASS-associated ILD and/or myositis and as it would be extremely unusual for the disease to flare so soon after receiving such significant immunosuppression. Other cases of lung and cardiac disease linked to trastuzumab generally occurred earlier (within 6 weeks of the introduction of the drug) than what is reported in the present case; however, it is possible that the concurrent use of cyclophosphamide resulted in delayed presentation. Nonetheless, this patient flared shortly after the introduction of trastuzumab and improved on the cessation of the monoclonal antibody along with additional immunomodulatory therapy. This case highlights a potential risk of HER-2 therapy for breast cancer in patients with known overlap between CTD and ILD. It is known that epidermal growth factor receptors are widely expressed in most human tissues and have an important function in cell signaling with roles in coordinating myoblast differentiation and innate immune responses (6-7). We hypothesize that the loss of regulation within these pathways contributed to the disease flare reported in our patient.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declares that this study has received no financial support.

References
4. Taus-García Á, Sánchez-Font A, Servitja-Tormo S, Pijuan L, Maigues-Llácer JM, Curull V. Organizing Pneumonia Associated with the Use of Trastuzumab. Archivos de Bronconeumología 2010; 46: 442-44. [CrossRef]