

Fever, Rash and Acute Inflammatory Polyarthritits in a Breast Cancer Patient after Trastuzumab Treatment: a Case Report

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Abstract

Trastuzumab, a humanized monoclonal antibody, is indicated for the treatment of early or metastatic breast cancer. Serum sickness-like reaction is mostly drug-induced and characterized by the presence of fever, rash and arthritis. There are no reports of breast cancer patients developing serum sickness-like reaction after receiving trastuzumab. We report herein the case of a breast cancer patient in whom its use was temporally related to the development of an acute inflammatory polyarthritits and rash. (J Intern Med Taiwan 2014; 25: 432-435)

Key Words: Serum sickness-like reaction, Trastuzumab, Breast Cancer

Introduction

Trastuzumab (Herceptin), a humanized monoclonal antibody against the extracellular domain of human epidermal growth factor receptor 2 (HER2), is indicated for the treatment of HER2-positive early or metastatic breast cancer¹. To the best of our knowledge, there are no case reports of serum sickness-like reaction associated with trastuzumab in breast cancer patients. We report a case in which the introduction of trastuzumab as adjuvant treatment for carcinoma of the breast was followed by the development of fever, rash and acute inflammatory arthritis.

Case report

A 46-year-old premenopausal female presented

to the hospital with acute onset of fever, rash, bilateral conjunctival congestion and multiple arthralgia shortly after the 8th infusion of trastuzumab. Eleven months prior to this presentation, the patient was diagnosed with HER2-positive infiltrating ductal carcinoma of the right breast (stage T2 N2 M0) and underwent a modified mastectomy. She had been healthy without a history of diabetes, hypertension or other major systemic disease. Her chemotherapy regimen consisted of a combination of epirubicin, and docetaxol plus cyclophosphamide for 6 courses, followed by trastuzumab 330g infusion every 3 weeks and tamoxifen 10mg bid.

The day after the 7th infusion of trastuzumab, she experienced multiple arthralgia without fever and chills. She went to local medical clinics where symptomatic treatment was given and the symptoms

later subsided. Shortly after the 8th infusion, bilateral conjunctival congestion, multiple arthralgia and fever developed.

On presentation, she reported itching rash in the trunk area and her bilateral conjunctivas were red and swollen (Fig. 1). There was no itching, eye pain, or discharge, but conjunctival injection on the bilateral eyes. There were erythematous patches on her trunk. The joints of the bilateral shoulders, right elbow, bilateral metacarpal-phalangeal and proximal interphalangeal joints were swollen, tender and warm. She had a fever of 38.2°C, but the rest of the vital and physical examinations were unremarkable. Laboratory studies showed white cell count of 12850/ul, eosinophil 3%, ESR 103mm/hr, CRP 19.92mg/dl, AST 27Unit/L, BUN 6.8 mg/dl, Cr 0.8 mg/dl, creatinine kinase 119Unit/L, uric acid 5mg/dl, ferritin 136 ng/ml, and negative urinalysis study. Her bilateral hand and C spine X-rays showed no abnormalities. Bone scan revealed no metastatic lesion. Infectious



Figure 1. Multiple purpuric macules and confluent patches on the trunk.

disease workup, including the influenza antibody test, HBsAg, anti-HCV, anti-HIV, blood and urine cultures was negative. Immune laboratory workup including C3, C4, antinuclear antibody, anti-cardiolipin antibody, anti SS-A, anti SS-B, rheumatoid factor, anti-CCP antibody, IgG, IgM, and IgA were within normal range.

In light of her recent treatment with trastuzumab, presenting symptoms, and negative infectious workup, a presumptive diagnosis of serum sickness-like reaction was made, due to the triad of fever, arthritis and erythematous rash following repeated drug exposure. She had gradual improvement with complete resolution of polyarthritid swelling, rash and conjunctival congestion after 21 days of prednisone 30mg/d treatment. Tamoxifen was reused after discharge without recurrence of symptoms. Trastuzumab was discontinued given our concern that the patient's symptoms may represent an adverse drug reaction.

Discussion

Various musculoskeletal manifestations can develop in a cancer patient, for reasons that include metastasis to the bones, paraneoplastic syndrome and altered immune reactions that cause rheumatic and neoplastic diseases, or adverse reactions to chemotherapy². Paraneoplastic syndromes are systemic or organ-related functional tumor-associated changes that arise distant to the tumor. Paraneoplastic rheumatic disorders generally precede the diagnosis of malignancy, the clinical course usually parallels that of the primary tumor, and in most cases treatment of the tumor resolves the paraneoplastic symptoms.³ The symptoms in this case begins after surgery, chemotherapy and 8th infusion of Trastuzumab, which implies that the diagnosis of paraneoplastic syndromes unlikely.

Serum sickness, first coined in 1905 by von Pirquet and Schick, is a type III hypersensitivity reaction induced by the deposition of circulating

immune complex in blood vessels and other tissues, complement activation and the subsequent inflammatory response.⁴ Serum sickness is frequently induced by administration of foreign proteins such as antithymocyte globulin or horse serum (utilized as an antiserum).⁵ Serum sickness-like reaction, first described by Murray et al in 1980, is most frequently drug-induced and characterized by the presence of fever, rash, and joint involvement.⁶ Unlike the serum sickness, the pathophysiology of serum sickness-like reaction is not fully understood, and is not associated with circulating immune complexes, hypocomplementemia or vasculitis.

Monoclonal antibodies are generally well tolerated in patients, though some acute reactions can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the monoclonal antibody, serum sickness-type, tumor lysis syndrome and cytokine release syndrome⁷. The most common treatment-related adverse events of trastuzumab were chills (25% of patients), asthenia (23%), fever (22%), and pain (18%)². Unlike rituximab, most hypersensitivity reactions to trastuzumab occurred after multiple exposures⁸.

The diagnosis of serum sickness-like reaction is based on clinical findings. The most frequent findings in serum sickness-like reaction are urticarial lesions (pruritic and migratory), fever, malaise, myalgia, and polyarthritis.⁹ Notable laboratory abnormalities include an elevated ESR, CRP and leukocytosis,¹⁰ which are compatible with this case.

Generally, serum sickness-like reaction has a benign clinical course and resolves in a few days, though cases of several weeks' duration also have been reported. Antihistamines and steroids have been used in some patients with satisfactory results as in our case, though controlled clinical data have not been reported.

Serum sickness-like reaction can present with

a variety of signs and symptoms, which may be of concern as an infectious process¹¹. Therefore, initiation of treatment is usually delayed until an infectious process is ruled out. In the interim, most patients receive empiric treatment with antibiotics as with our patient.

The close temporal relationship with the use of trastuzumab suggests the possibility that a drug side-effect may have been responsible for the acute arthritis and rash. The resolution of symptoms on ceasing the drug was striking. To our knowledge, trastuzumab has never been reported as a cause for serum sickness-like reaction. We have described a case in which trastuzumab appeared to be associated with the development of an acute inflammatory polyarthritis, rash and conjunctivitis.

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乳癌病患使用賀癌平後產生發燒、紅疹和發炎性關節炎：個案報告

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摘要

類血清病反應的主要表現是發燒、皮疹、關節疼痛和淋巴結腫大，一般發生在用藥後。賀癌平是單株抗體，廣泛使用於治療乳癌，但尚未有使用賀癌平治療乳癌後產生類血清病反應的個案報告。我們在此報告一位病患，在使用此藥後發生發燒、急性發炎性關節炎和紅疹。