

# Trastuzumab in the Treatment of Invasive Ductal Carcinoma of the Breast Induces Severe Edema: A Case Report

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## Case report

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# Abstract

## Background

Trastuzumab, a monoclonal antibody which binds to the extracellular domain of HER2, is the first biological drug approved for the treatment of HER2-positive breast cancer. However, trastuzumab exhibits a series of adverse reactions in clinic, including cardiac toxicity, nerve damage, mild edema, abnormal liver function, thrombocytopenia, etc.

## Case presentation

We reported an invasive ductal carcinoma of the breast patient with single dose trastuzumab treatment developed a rare severe edema in patient's neck, face, chest, abdomen, and both upper limbs. One month after trastuzumab administration, the patient was given methylprednisone (80 mg/day) for 5 days. The edema in patient's neck, face and both upper limbs was mildly reduced compared with before, but patient's CT image showed no significant reduction of edema.

## Conclusion

Trastuzumab has an adverse reaction of edema, but this severe edema is extremely rare. It is important to increase awareness of serious adverse reactions among oncologist, and treat such serious adverse reactions at an early stage may reduce further damage.

# Introduction

Overexpression of human epidermal growth factor receptor 2 (HER2) is implicated in the pathophysiology of breast cancer and represents a clinically relevant biomarker for its treatment[1]. Trastuzumab, a monoclonal antibody which binds to the extracellular domain of HER2, is the first biological drug approved for the treatment of HER2-positive breast cancer. However, trastuzumab also exhibits a series of adverse reactions in clinic, including cardiac toxicity, nerve damage, edema, abnormal liver function, thrombocytopenia, etc. In this case report, we reported an invasive ductal carcinoma of the breast patient with only once trastuzumab treatment developed severe edema, which implied the potential allergic reaction of trastuzumab remains to be further concerned in clinical application.

# Case Report

A 46-year-old female underwent surgery in April 2020, and was diagnosed as invasive ductal carcinoma of the breast on the right side. After surgery, the patient was given 1 cycle of paclitaxel combined with cyclophosphamide and doxorubicin treatment, and 2 cycles of docetaxel and epirubicin combined with cyclophosphamide therapy. After three chemotherapy sessions, trastuzumab (440 mg) was administrated as a single dose on June 25th. Subsequently, the patient developed edema symptoms, which gradually worsened until July 15th, on which patient had severe edema in the neck, face, chest,

abdomen, and both upper limbs (Figure 1). The hands of the patient presented the most remarkable edema symptoms, where the epidermis was transparent and tight (Figure 2), and the skin temperature is high. In addition, the patient had obvious pharyngeal edema and could only take a small amount of fluid diet. The patient was unable to stand and walk due to motor and sensory nerve damage in both upper and lower extremities induced by trastuzumab administration. Moreover, the patient developed an immunocompromised state, who are susceptible to pulmonary infection. Because the hospital patient originally visited could not deal with such severe situation, the patient visited our hospital for further treatment. Our hospital carries out whole-hospital consultation, and prestigious dermatologists from other hospitals were invited to participate in the consultation. Physicians and specialists considered the edema of the patient with unknown origin and excluded angioedema. Due to the severe edema, biopsy could not be performed in the patient to further clarify the etiology. One month after administration of trastuzumab, the patient was given methylprednisone 80 mg/day for 5 days. The edema in neck, face and both upper limbs of the patient was mildly reduced compared with before, but the follow-up CT showed no significant reduction in edema.

## Discussion And Conclusion

Up to 15-20% of patients with early breast cancer have tumors that exhibit overexpression, amplification, or both, of the HER2 receptor or oncogene[2]. Trastuzumab has a major effect in reducing recurrence and death in patients with this type of early breast cancer[3]. Although there are other targeting HER2 agents currently available for patients of HER2-positive breast cancer, such as pertuzumab, trastuzumab remains the gold standard for treatment of this disease subtypes. Accumulating evidences have shown that trastuzumab played a critical role in immune regulation to achieve an anti-tumor efficacy. It can either induce immune-mediated anti-tumor effect, or increase the possibility of synergistic regulation of the immune system. In addition, trastuzumab combined with chemotherapy can enhance chemotherapy-induced cytotoxicity by decreasing DNA repair activity and increasing apoptosis[4]. It has been reported that when trastuzumab was applied in conjunction with adjuvant chemotherapy, the advantage of 1-year treatment was even more significant[4].

Nonetheless, trastuzumab also exhibited some side effects, mainly manifested as heart damage. Peripheral edema and lymphedema are commonly observed, but mainly exhibit as local edema. To our knowledge, no cases of diffuse edema in multiple parts of the body have been reported previously. We considered that the severe edema in the reported patient might be related to the trastuzumab-induced allergic reaction, which resulted in endothelial cell damage and inflammatory cytokines production. Subsequently, it could cause decreased vascular wall integrity, increased vascular permeability, aberrant hemorheology, so that blood flow into peripheral tissues leading to edema[5]. Since allergies could induce increased energy consumption, insufficient protein intake will further aggravate the edema. Another possibility is that due to protein exudation into the infarct area combined with membrane rupture that resulting in increased permeability. It leads to regional blood flow suppression, and irreversible tissue damage is occurred[6]. In addition, allergic reaction can further aggravate oxidative stress, leading to angiotensin II upregulation, which in turn results in more inhibitory signals and enhanced oxidative

stress[1]. Furthermore, it can activate NADPH oxidase, which lead to mitochondrial dysfunction and cell death. In this case report, after 5 days of treatment with methylprednisone, the edema in neck, face and both upper limbs of the patient were mildly reduced. These suggested that if hormone therapy is given at the early stage, the patient may not experience severe edema later on.

Our report suggests that trastuzumab administration in breast cancers may cause severe allergic reactions, which should be concerned in clinical application. Individual patient may have different sensitivities to drugs, and the occurrence of adverse reactions are various. In clinical application, the early-stage adverse reactions induced by drug administration should be paid great attention, so as to avoid the possibility of subsequent serious adverse reactions.

## **Declarations**

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### **Authors' contributions**

QW, YA, JW collected data. YZ, JH radiological selection. HZ, JZ wrote the manuscript. All authors contributed to the article and approved the submitted version.

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### **Availability of data and materials**

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### **Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

Positive.

### **Competing interests**

There are no conflicts of interest.

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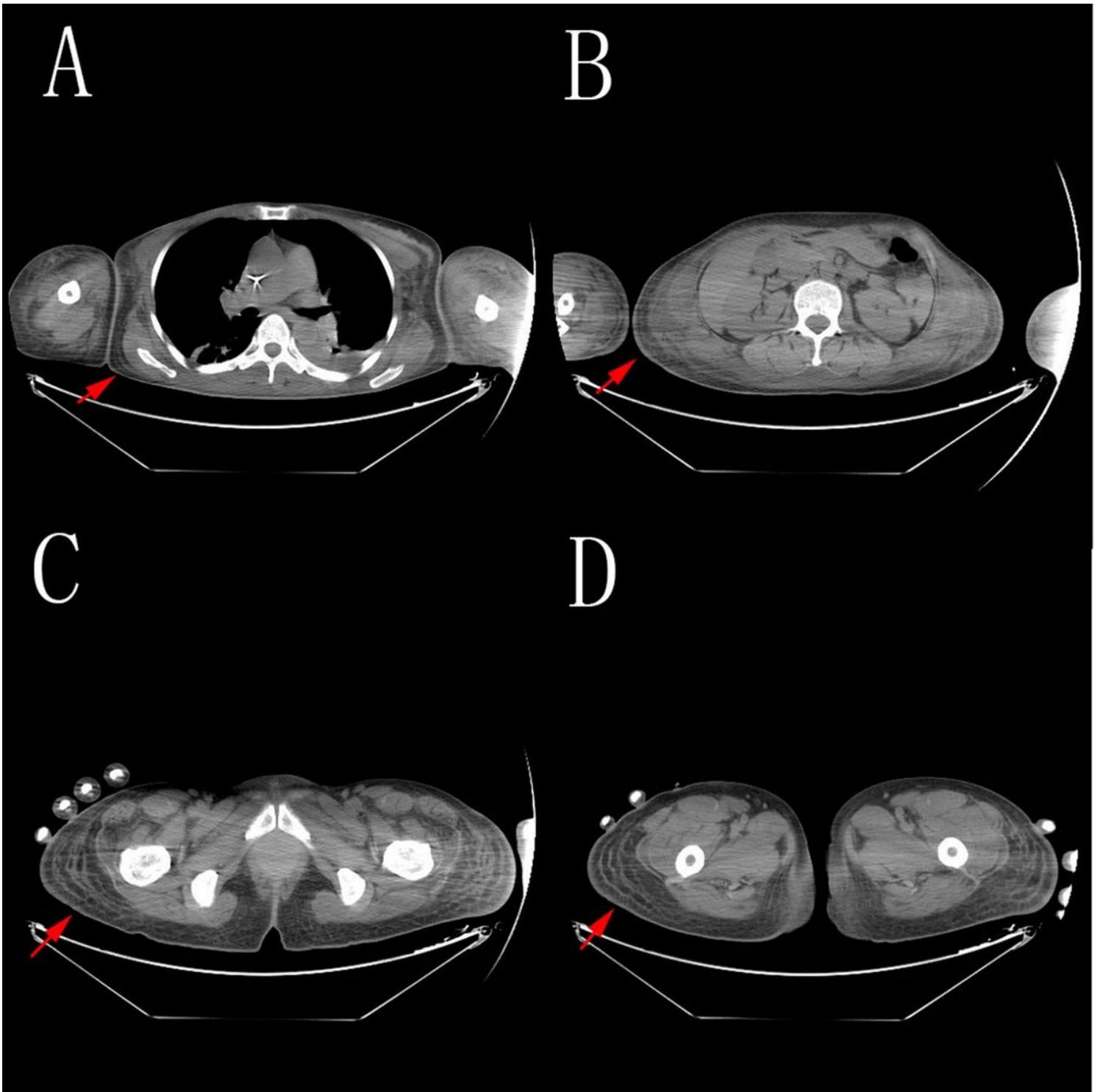
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## Figures



**Figure 1**

Imaging of CT examination. The patient received CT examination on August 5th, 2020. A. Edema in both upper limbs and chest. B Edema in abdominal. C Edema in buttocks . D Edema in thigh.



**Figure 2**

Trastuzumab-induced edema in hands of the patient. A. The picture of edema in hands of the patient before methylprednisolone administration. B. After treatment with methylprednisolone (80 mg/day, for 5days), the edema of the patient was relieved, the skin tightness was decreased, the epidermis was desquamated, and the pigmentation was observed.