Toxic pneumonitis induced by trastuzumab as a potentially fatal event: a case report

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ABSTRACT

Background: Trastuzumab is a widely used and well-tolerated drug. Pulmonary toxicity has been described; however, the low incidence, the variability at presentation, and the nonspecific characteristics often make it an exclusion diagnosis.

Case presentation: We present the case of a 62-year-old women admitted to our service with fever and shortness of breast after treatment with trastuzumab. From the study performed, no other cause was found to explain the event and the patient kept worsening until the diagnosis was established.

Conclusion: Although pneumonitis is a rare side effect of trastuzumab administration, early recognition and appropriate therapy are crucial and may be lifesaving.

Keywords: Breast cancer, trastuzumab, adverse reactions, pulmonary toxicity, case report.

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Background

Breast cancer, the most common in women, is one of the tumors with the highest incidence rate, which causes a large number of patients to be diagnosed and treated, with a strong impact in terms of public health [1]. Fortunately, over the past few years, scientific developments, mainly in the field of molecular biology, have allowed the emergence of new therapies, increasingly directed at tumors' characteristics.

Trastuzumab, a recombinant anti-human epidermal growth factor receptor 2 (HER2) antibody, which appeared in the 1990s for the treatment of metastatic breast cancer, and later came to show effects at early stages, completely altered the natural history of the disease, greatly improving patients' prognosis. Thus, despite the more recent emergence of other agents, such as pertuzumab, it continues to be a gold standard in the treatment of breast cancer, with different therapeutic purposes [2,3]. Trastuzumab is a widely used and well-tolerated drug. The main adverse effects are known and are related to gastrointestinal changes, neutropenia, arthralgia, myalgia, asthenia, and anorexia. Some patients have more serious complications, mainly anaphylactic and cardiac [4]. It is reported that about 15% of the patients can develop infusion reactions of moderate severity, but can be easily managed. Cardiac toxicity is mainly associated with a decrease in the left ventricular ejection fraction, which tends to be reversible with the suspension of the drug, unlike what happens with other cytotoxic agents, such as anthracyclines. It is a known and documented adverse effect that only requires patients' monitoring with serial echocardiograms throughout treatment [5,6]. Pulmonary toxicity is also described in the characteristics of the drug; however, the low incidence, the variability at the beginning of presentation, and the nonspecific characteristics tend to hinder and delay the diagnosis, making it often an exclusion diagnosis [7]. Despite being a rare event, it is potentially fatal, which makes alerting health professionals important.

Case Presentation

Female patient, 62-year-old, domestic. Personal history of hypertension and menopause at the age of 50 years due to hysterectomy with bilateral annexectomy. Medicated with lisinopril 5 mg per day and pantoprazole 20 mg per day.
In October 2020, she was diagnosed with a locally advanced invasive ductal carcinoma of the left breast, with no evidence of distant disease, clinical stage T3N+. Baseline echocardiogram showed a left ventricular ejection fraction of 79%. In a multidisciplinary group meeting, neoadjuvant treatment was decided with a schedule of 4 cycles of dose-dense anthracycline and doxorubicin,

followed by 12 cycles of weekly paclitaxel with dual-anti-HER2 blockage with pertuzumab and trastuzumab.

The first phase of treatment was carried out without complications and with excellent tolerance. During the first cycle of the second phase of the treatment, while trastuzumab was being perfused, the patient had a feverish peak (39.5°C) with shivering. She was hospitalized for monitoring and, given the resolution of the event, completed the treatment, and was discharged the next day. She was reevaluated 3 days later and referred another isolated febrile peak (39°C) the previous day, without focalizing complaints.

On clinic examination, the patient was conscious and orientated, with stained and hydrated mucous membranes, eupneic, without changes in pulmonary auscultation, innocent abdomen, without peripheral edema. Analytically, C-protein reaction of 77 mg/l (N, <5 mg/l) and lymphopenia of 300/µl, without neutropenia were reported. Previous echocardiogram, performed after completing the anthracycline cycle, revealed an ejection fraction of 64%. Thus, she was hospitalized to continue investigation.

From the study performed, there were no agents isolated in the blood and urine cultures. She was started on empirical antibiotics - amoxicillin/clavulanic acid and ciprofloxacin. However, after 4 days, she maintained fever and reported asthenia and the onset of nonproductive cough. Despite no major changes in blood analysis, it was decided to escalate antibiotics to piperacillin and tazobactam. New cultural tests were carried out which remained negative, H1N1 negative, with viral serologies without changes. Clinically persistent fever and dyspnea with hipoxia were reversed with oxygen supply. After 7 days, antibiotics were changed to meropenem and vancomycin. A chest CT was performed and revealed "areas of densification in scattered and bilateral ground glass, accompanied by interstitial thickening with a reticular pattern." (Figure 1).

There was no evidence of significant changes in brochofibroscopy. A sparse flora of *Candida albicans* was isolated, but the patient showed no improvement after the onset of fluconazole.

In a multidisciplinary reunion with oncologists, pulmonologists, infectologists, and immunoalergologists, the exclusion diagnosis of toxic pneumonitis induced by trastuzumab was assumed. The antifungal was stopped, and the patient started corticosteroid therapy (prednisolone 1 mg/kg/day). Since that time, she remained apyretic and showed a rapid improvement in complaints of dyspnea and normalization of pulmonary auscultation, with withdrawal of oxygen supply.

After 21 days, the patient was discharge with a regimen of corticosteroid therapy in progressive weaning. She showed favorable clinical and analytical evolution and was able to resume neoadjuvant treatment with anthracycline and doxorubicin without any meaningful toxicity. One month after this event, chest CT revealed full resolution of the previous abnormalities (Figure 2).

Discussion

Trastuzumab's pulmonary toxicity is referred in the drug literature not only as an adverse event, but also as special warnings and precautions: "After the marketing of Herceptin, serious pulmonary events have been reported with the use of Herceptin. These events were occasionally fatal. In addition, cases of interstitial lung disease including pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, breathing difficulties, acute pulmonary edema, and respiratory failure have been reported. These events may occur as part of an infusion reaction or as a late onset adverse event. Care should be taken with pneumonitis, especially in patients who are being treated concomitantly with taxanes" [8].

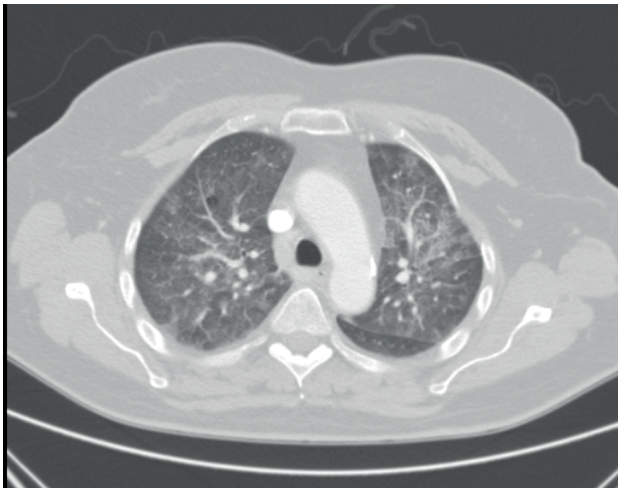

Figure 1. *Chest CT at diagnosis.*

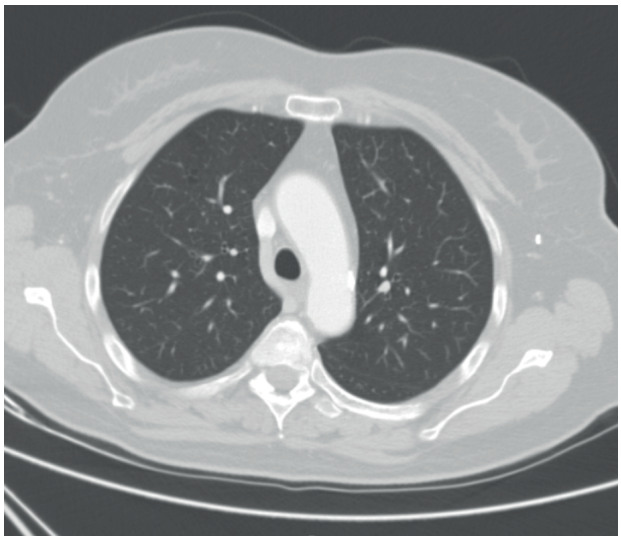

Figure 2. *Chest CT after treatment.*

Despite the wide use of trastuzumab in clinical practice, toxic pneumonitis is a rare event, with an incidence of 0.4%-0.6%, and as such, there are few cases described [9]. In addition to the low incidence, the variability in the onset of installation, as well as the clinical presentation, contributes to the delay and difficulty in its diagnosis. Trastuzumab-induced pneumonitis may present with rapidly progressive pulmonary infiltrates and respiratory failure after receiving one dose of trastuzumab or after 6 weeks of therapy.

By 2020, approximately 10 cases of toxic pneumonitis induced by trastuzumab have been described. Although nonspecific, the main symptoms were dyspnea, hypoxia, dry cough, and fever. Virtually, all patients had chest CT abnormalities with bilateral ground-glass opacifications. The prompt institution of corticosteroid therapy (1 mg/kg/day) resulted in a rapid clinical improvement, within 48 hours [10-15]. Given the severity, and possible irreversibility of the pulmonary changes, the rapid diagnosis of trastuzumab-induced injury is essential.

Conclusion

Our patient presented with an insidious and nonspecific clinical case of fever, cough, dyspnea, and hipoxia that led to the raise of other hypotheses before establishing the exclusion diagnosis of toxic pneumonitis induced by trastuzumab. When trastuzumab-induced pneumonitis is suspected, the drug should be discontinued and, if the diagnosis is confirmed, it should be permanently discontinued. Luckily, our patient had a full recovery.

Although pneumonitis is a rare side effect of trastuzumab administration, it is important to be aware of this specific toxicity because early recognition and appropriate therapy may be lifesaving.

What is new?

Trastuzumab is a widely used and well-tolerated drug. The main adverse effects are known and easily manageable. However, pulmonary toxicity, although rare, exists and can be potentially fatal. The purpose of this case report is to alert health professionals to this reality and allow a good management of similar situations.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written and informed consent was taken from the patient to publish this case report.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Female, 62-year-old
2	**Final diagnosis**	Toxic pneumonitis induced by trastuzumab
3	**Symptoms**	Cough, fever, and dyspnea with hipoxia
4	**Medications**	Prednisolone 1 mg/kg
5	**Clinical procedure**	Diagnosis and treatment
6	**Specialty**	Oncology