CASE REPORT

Trastuzumab-Induced Severe Thrombocytopenia: A Case Report and Literature Review

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Abstract We present a 29-year-old woman with pT2N0M0 breast cancer, histological diagnosis of invasive ductal carcinoma, ER and PR low positive, and HER-2 (3+). The patient developed trastuzumab-induced thrombocytopenia in 6 hours after an intravenous infusion of trastuzumab at the second cycle of trastuzumab treatment with the symptom of abnormal uterine bleeding. Laboratory exam revealed a sharp drop of platelet count down to $3 \times 10^9/L$. With the treatment of single-donor platelet transfusions, glucocorticoids, oxytocin and thrombopoietic drugs, the platelet count recovered completely in 11 days. This case was confirmed to be severe thrombocytopenia induced by trastuzumab, and retreatment with trastuzumab was not attempted. With increasing clinical utilization of trastuzumab, clinicians are likely to encounter more life-threatening trastuzumab induced severe thrombocytopenia. By this case report and literature review, we hope to increase the awareness, attach the attentions to this condition, and help with the effective treatment.

ACCORDING to the Global Cancer Statistics 2018,^[1] breast cancer is the most common cancer worldwide, and it is also the most common malignant tumor in Chinese women.^[2] Studies have shown that about 15%-20% of breast cancer patients overexpress the human epidermal growth factor receptor 2 (HER2) gene.^[3] Functions

of the HER2 gene include regulating cell proliferation, transformation, and apoptosis, all of which are related to tumor invasiveness. As such, HER2-positive breast cancer patients are at high risk of recurrence and metastasis.

Trastuzumab is a recombinant human monoclonal antibody against HER2, which selectively acts on the extracellular part of HER2 and inhibits the overexpression of HER2.^[4] A number of clinical studies, including the NASBP-31, N9831, BCIRG006, and HERA trials, have shown that trastuzumab significantly improves the survival of HER2-positive breast cancer patients, and thus trastuzumab has become a recommended treatment for HER2-positive patients.^[5] Trastuzumab

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was included in the Chinese National Medical Insurance Catalogue in July 2017. With sharp decreases in the price of trastuzumab, more and more Chinese HER2-positive breast cancer patients can afford the medication.

The main side effects of trastuzumab are cardiotoxicity and anaphylaxis. Severe thrombocytopenia caused by trastuzumab is rare; therefore, it is important and helpful to report every case in order to increase vigilance for the complications and optimize therapeutic regimens.

To the best of our knowledge, there have only been 9 cases of trastuzumab-induced thrombocytopenia published in literature.^[6-14] Herein, we report a case from our medical center, with literature review aiming to establish the most appropriate treatment.

CASE DESCRIPTION

A 29-year-old female with a painless palpable mass in her right breast was hospitalized in the Breast Center of Nanfang Hospital in June 2019 for histopathological diagnosed of invasive ductal carcinoma (IDC) by core needle biopsy. Physical examination revealed a palpable mass in the upper outer quadrant of the right breast. Breast imaging showed a 3.5 cm mass with mammographic microcalcification, and axillary node was negative. The patient declined the sentinel lymph node biopsy (SLNB) and the stage 1 breast reconstruction for personal reasons, and underwent a modified radical mastectomy in June 2019. The surgical pathology reported an invasive ductal carcinoma (IDC) of 3.5 cm in diameter, histological grade 3, and all 21 axillary lymph nodes examined were negative. Immunohistochemistry testing (IHC) revealed the tumor was estrogen receptor (ER) low-positive (2% of nuclei stained), progesterone receptor (PR) low-positive (3% of nuclei stained), and HER2 positive (3+). Full staging workup revealed no evidence of distant metastasis, and the final disease stage was pT2N0M0, IIA.

Subsequently, the patient received 6 cycles of doxorubicin and paclitaxel chemotherapy [doxorubicin: 60 mg/m² intravenous infusion (IV) on day 1; paclitaxel: 175 mg/m² over 3 hours IV on day 1; cycled every 21 days for a total of 6 cycles]. The patient completed chemotherapy in October 2019, and was subsequently treated with trastuzumab (loading dose of 8 mg/kg IV, day 1 for the first cycle, followed by 6 mg/kg IV, day 1, every 21 days for 1 year). Because the tumor was ER

and PR positive, she was put on tamoxifen 20 mg daily after completion of chemotherapy. Her menstrual cycle became irregular during endocrine therapy.

The first dose of trastuzumab was administered on November 7, 2019, and her platelet count was 180×10⁹/L before the treatment. No complications occurred and no abnormalities were noted over the next 20 days. On November 28, 2019 she received the second dose trastuzumab, with platelet count of 74×10⁹/L prior to the administration, and then was discharged. Six hours later she experienced abnormal uterine bleeding and was re-admitted to hospital. Laboratory examinations revealed her platelet count was 3×10⁹/L, liver function, renal function, clotting and d-dimers were normal. The patient was not exposed to medications other than tamoxifen, and there were no reports in the literature on tamoxifen causing severe thrombocytopenia.

After treatment with oxytocin (10 IU, micro-pump 0.04 IU/min, IV), the symptom of uterine bleeding relieved. She was also treated with a single-donor platelet (SDP) transfusion 2 U on the first day, 1 U on the second day, and 1 U on the fourth day (1 U can theoretically increase the platelet count by 20×10⁹/L), dexamethasone and recombinant human interleukin-11 (IL-11) 50 µg/kg daily, recombinant human thrombopoietin (rhTPO) 300 U/kg daily. In 11 days, her platelet count gradually increased to 123×10⁹/L (**Figure 1**).

Considering that the severe thrombocytopenia was likely induced by trastuzumab, it was discontinued. She was instead treated with ovarian suppression (goserelin 3.6 mg, subcutaneous injection, every 28 days for 5 years), along with tamoxifen 20 mg daily for 10 years.

DISCUSSION

Diagnosis of drug-induced thrombocytopenia is usually made by exclusive method. In 1998, George *et al.*^[15] established criteria to determine the likelihood of drug-induced thrombocytopenia: 1) therapy with the candidate drug precedes thrombocytopenia, and recovery from thrombocytopenia follows discontinuing the drug; 2) the candidate drug is the only drug used before the onset of thrombocytopenia, or other drugs are continued or reintroduced after discontinuation of the candidate drug, the platelet count sustains normal; 3) other causes for thrombocytopenia are excluded;

Figure 1. Platelet counts in blood by day during the second cycle of trastuzumab therapy in a 29-year-old HER2-positive breast cancer patient with trastuzumab induced severe thrombocytopenia.

4) re-exposure to candidate drug results in recurrent thrombocytopenia. Drug-induced thrombocytopenia should be suspected in any patient who presents with acute thrombocytopenia of unknown cause.^[16] If the causative medication is stopped, symptoms usually resolve within 1 or 2 days, and the platelet count returns to normal in less than a week.

This patient fulfilled the first 3 criteria for diagnosis of drug-induced thrombocytopenia. Trastuzumab was the only medication administered, thus it was most likely cause of the thrombocytopenia. Because of the life-threatening thrombocytopenia, trastuzumab was completely discontinued, and she was treated with endocrine therapy (ovarian suppression plus tamoxifen). As of the preparation of this report, the patient is alive and well with no tumor recurrence.

Luo *et al.*^[14] reported another case from our center in 2019. The patient was found to have severe thrombocytopenia 10 days after administration of paclitaxel and trastuzumab. Because paclitaxel is known to cause thrombocytopenia by suppressing hematopoiesis, for the next cycle she was only given trastuzumab. Severe thrombocytopenia again occurred, and thus the diagnosis was trastuzumab-induced thrombocytopenia. The treatment with trastuzumab was discontinued, and she subsequently received chemotherapy with paclitaxel and carboplatin for 4 cycles. Although both paclitaxel and carboplatin could cause severe thrombocytopenia, her platelet count remained normal after the trastuzumab was stopped. She received radiation therapy (50 Gy in 25 fractions) one month after chemotherapy and died of brain metastasis 2 years later.

By literature review, there were 9 reported cases of thrombocytopenia induced by trastuzumab (**Table**

1).^[6-14] Of 10 patients in total, 6 were over 50 years old, the youngest was 29 years old. In addition, 5 cases developed acute thrombocytopenia shortly (from 10 hours to 4 days) after the first trastuzumab infusion, and reoccurrence mostly happened on the third day after the second injection. Delayed thrombocytopenia occurred in 3 patients (10, 19, 21 days after treatment), and in one patient it only occurred after the second administration of trastuzumab. Petechial rash was the first presenting symptom mostly; other symptoms included nose bleeding, dental bleeding, and uterine bleeding. Most patients recovered after treatment with glucocorticoids, immunoglobulin, and SDP transfusions.

The etiology of drug-induced thrombocytopenia is complex, and at least 6 distinct pathological mechanisms having been suggested, including hepten-dependent antibodies, drug-dependent antibodies, fibrin-induced thrombocytopenia, drug-specific antibodies, autoantibody induction, and immune complexes.^[17] For the current case, because the platelet count dropped sharply, we made prompt treatment focusing on to increase platelet count to a safe level, so did not test antibodies and further perform other studies to investigate the underlying mechanisms, which was a limitation of our study.

According to the American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia,^[18] immune thrombocytopenia is an acquired autoimmune disorder characterized by a low platelet count caused by platelet destruction and impaired platelet production. Corticosteroids are recommended for patients with a platelet count $<30 \times 10^9/L$. The Chinese Guidelines for Treatment of Adult Primary Immune

Table 1. Clinical information of the trastuzumab-induced thrombocytopenia cases reported in the literature

Case No.	References	Year*	Age (y/o)	Cycle	Onset time	Symptom (s)	Platelet# ($\times 10^9/L$)	Treatment	Recovery time
1	Cathomas R, <i>et al.</i> ^[6]	2007	54	1	4 days	Nose bleeding and petechiae	3	Immunoglobulin; methylprednisolone	7 days
2	Parikh O, <i>et al.</i> ^[7]	2006	56	1	10 hours	Petechiae	2	Immunoglobulin	7 days
3	Jara Sanchez C. <i>et al.</i> ^[8]	2008	37	1	1 day	Petechiae	3	Gamma globulin; glucocorticoids; SDP transfusion	4 days
				2	3 days	Petechiae	12	Splenectomy; glucocorticoids	7 days
4	Drudi F, <i>et al.</i> ^[9]	2010	NR	1	19 days	Petechiae	7	Immunoglobulin; dexamethasone; SDP transfusion	Death [†]
5	Mantzourani M, <i>et al.</i> ^[10]	2010	56	1	3 days	Nose bleeding and petechiae	5	Immunoglobulin	5 days
				2	3 days	NR	28	NR	10 days
				3	3 days	NR	128	NR	N/A
6	Pino MS, <i>et al.</i> ^[11]	2012	70	1	1 day	Petechiae and ecchymosis	0	Immunoglobulin; methylprednisolone; SDP transfusion	6 days
				2	5 days	Tiredness	28	Ethamsylate [‡]	7 days
				3	4 days	None	19	Ethamsylate; rhTPO	9 days
				4	4 days	None	39	rhTPO	8 days
7	Zeng RC, <i>et al.</i> ^[12]	2010	57	5	1 day	Tiredness and dental bleeding	20	Ethamsylate	8 days
				6	N/A	None	Normal	N/A	N/A
				7	3 days	Dental bleeding	60	Ethamsylate	8 days
				8	1 day	Dental bleeding	39	Ethamsylate	10 days
8	Miarons M, <i>et al.</i> ^[13]	2015	70	4	NR	None	39	Prednisone	4 weeks
9	Luo Q, <i>et al.</i> ^[14]	2016	39	1	10 days	Petechiae	3	SDP transfusion; ethamsylate; IL-11	5 days
				2	7 hours	Petechiae	9	Gamma globulin; SDP transfusion; ethamsylate; IL-11	4 days
10	Current case	2019	29	1	21 days	None	74	Observation	N/A
				2	6 hours	Uterine bleeding	3	Oxytocin; SDP transfusion; dexamethasone; IL-11; rhTPO	11 days

*The year when the drug-induced thrombocytopenia was diagnosed. #The lowest value of the platelet count. ‡Ethamsylate was used to prevent spontaneous bleeding. †The patient had brain metastasis, and thrombocytopenia persisted until she died for tumor progression 2 months later. SDP, single donor platelet; N/A, not applicable; NR, not reported; rhTPO, recombinant human thrombopoietin.

Thrombocytopenia^[19] defines the severe thrombocytopenia when a platelet count drops below $10 \times 10^9/L$. Emergent treatment to elevate platelet to a safe level as quickly as possible is important for adults with severe thrombocytopenia. Interventions include discontinuation of the causative drug(s), high-dose methylprednisolone (1,000 mg/day for 3 days), intravenous immunoglobulin (1,000 mg/kg/day for 1-2 days), thrombopoietic drugs, either alone or in combination, and SDP transfusions.^[19]

For the patient presented herein, the platelet count dropped below $10 \times 10^9/L$, and developed life-threatening bleeding. The patient was treated with glucocorticoids, SDP transfusions, rhTPO, and IL-11. Then platelet counts returned to a safe level within 2 days. Therefore, we believe patients with drug-induced thrombocytopenia should stop using the possible inducing drug immediately; glucocorticoids, immunoglobulin and SDP transfusions could be applied for severe cases if necessary.

However, the decision on withdrawal of trastuzumab must base on clinical grounds. Of the 9 cases in the literature, trastuzumab was discontinued for the risk of thrombocytopenia in 7 cases, and the patients were re-challenged with trastuzumab in 2 cases. One of the 2 cases had a course of intravenous immunoglobulin at the first episode of trastuzumab induced thrombocytopenia, and the same condition reoccurred, but extinguished at the third cycle of trastuzumab infusion without any intervention;^[10] in the other case, the time interval between the 2 cycles of trastuzumab was prolonged, no dental bleeding symptoms were observed then.^[12] A number of other medications have been developed for the treatment of HER2-positive patients, such as lapatinib, neratinib, and pyrotinib. Whether these drugs could replace trastuzumab, and whether they may also pose a risk of thrombocytopenia remain to be determined. In 2009, Cathomas *et al.*^[6] reported a case of severe trastuzumab-induced thrombocytopenia. Trastuzumab was discontinued and the patient was treated with lapatinib (1,250 mg, daily) without recurrence of thrombocytopenia. Because just 1 mg or 2 mg lapatinib can cause a substantial drop in platelet, it is important to administer an appropriate low dose and closely monitor platelet count for 24 hours.^[16]

Though the severe thrombocytopenia caused by trastuzumab is rare, with increasing use of trastuzumab, it is foreseeable that this complication will be more likely to be encountered in clinical practice. Thus, clinicians need to be aware the possibility that trastuzumab could cause severe thrombocytopenia. When trastuzumab-induced thrombocytopenia is diagnosed, discontinuation of trastuzumab and the treatment with SDP transfusions, glucocorticoids, intravenous immunoglobulin, and thrombopoietic drugs, either alone or in combination, are recommended.

Conflict of interests

All authors declared no conflicting interests.

Compliance with ethics

Written informed consent from the reported patient was obtained.

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