Drug-induced thrombocytopenia induced by trastuzumab: a special challenge in a curable disease

Drug-induced thrombocytopenia can be caused by hundreds of medications, usually caused by immunoglobulins that recognize specific platelet membrane proteins in the presence of the sensitizing drug. If the causative drug is stopped, platelet count should return to normal in a short interval of time. In cancer patients, it can be easily overlooked because thrombocytopenia can have many other causes, and it is attributed to drug-induced marrow suppression and/or marrow replacement by tumor.

It has been described that drug-induced immune thrombocytopenia is associated with several chemotherapeutic agents (such as oxaliplatin [1, 2], fludarabine and irinotecan [3]) and with new targeted mAbs such as abciximab, infliximab and rituximab [4], but thrombocytopenia induced by trastuzumab is a very rare incident [5, 6].

We report the third case in the literature of this severe and potentially life-threatening complication associated to trastuzumab.

A 37-year-old woman underwent surgery with lumpectomy and sentinel node dissection for localized breast cancer in March 2008. Evaluation of specimen showed two tumors: apocrine carcinoma with areas of ductal carcinoma in situ of 18 mm and a second lesion of invasive ductal carcinoma, size 16 mm. The steroids hormone receptors were positive and human epidermal growth factor receptor 2 (HER2) (Herceptest; Dako Group, Carpinteria, CA) was amplified. Diagnosis of breast cancer stage I (pT1c pNsn0 M0) was made.

Adjuvant chemotherapy with taxotere, carboplatin and herceptin regimen, consisting of carboplatin (area under the curve 6 mg/ml-min), docetaxel (75 mg/m²) and trastuzumab at a loading dose of 8 mg/kg, every 3 weeks was initiated in May 2008. She received oral treatment with naproxen, ondansetron and omeprazol. Platelet count was 328 000 × 10⁹/l at the start of treatment. One day after the infusion, the patient turned to the emergency room where generalized petechiae were found, without spontaneous bleeding. The platelet count was 3000 × 10⁹/l, with normal leukocyte and hemoglobin count and routine biochemistry and clotting were anodyne. She was admitted and a platelet transfusion was administered. On the next day, her platelet count was 6000 × 10⁹/l. Because of intense headache without another neurologic symptom, a cranial computed tomography was made, and no abnormalities were seen. She was evaluated by the hematology team and other causes of thrombocytopenia were excluded. Treatment with dexamethasone 40 mg/day for 4 days and immune globulin (1 g/kg in 24 h) as proposed by Mazzucconi [7] was initiated with good response, and platelet levels remained within the normal range since the fourth day of treatment.

A modified second cycle (carboplatin omitted and trastuzumab at a dose of 6 mg/kg) was administered and 3 days later, her platelet count decreased to 12 000 × 10⁹/l. A bone marrow biopsy was obtained. It showed normal megakaryocytopoiesis and no signs of infiltration by tumor were found. Diagnosis of immune thrombocytopenia induced by trastuzumab was suspected. The patient underwent splenectomy. One week later, treatment with docetaxel, carboplatin and trastuzumab was reinitiated. Two days after the infusion, her platelet count was reduced again (13 000 × 10⁹/l). Again, she was given treatment with corticosteroids and her platelet count fully recovered in a couple of days. A third cycle of chemotherapeutic agents was administered after 21 days. At this time, we excluded trastuzumab infusion; a blood count was made after 4 days and her platelet count was in the normal range. Trastuzumab has not been administered since then. Diagnosis of trastuzumab-induced thrombocytopenia was made. The patient finalized adjuvant chemotherapy with docetaxel, adriamidine and cyclophosphamide, without hematologic complications. The patient was reexposed to omeprazol and ondansetron without a change in the platelet count. She began hormonal treatment and received radiotherapy to the breast and continues on follow-up.

Chemotherapeutic agents are known to typically cause thrombocytopenia by suppressing hematopoiesis, but they can also cause immune thrombocytopenia. This entity should be suspected in patients treated with such drugs if...
there is a sharp drop in the platelet count after exposure and if platelet levels return to normal quickly after drug suppression.

Diagnosis of drug-induced immune thrombocytopenia is usually made by exclusion. In their seminal work, George et al. [9] have proposed criteria and level of evidence for establishing a causative relationship in drug-induced thrombocytopenia. In this case, treatment with carboplatin, docetaxel and trastuzumab preceded thrombocytopenia. We excluded carboplatin and docetaxel as causal agents because only the reexposure to trastuzumab resulted in recurrent thrombocytopenia. Recovery was complete and sustained after the discontinuation of this drug. Other causes of thrombocytopenia were excluded.

There are several described mechanisms of pathogenesis of drug-induced thrombocytopenia [7, 8]. All of them have an immunologic reaction implicated, which can include hapten-induced antibodies, drug-dependent antibodies, glycoprotein IIb/IIIa inhibitors or drug-dependent antibodies. New targeted therapies like mAbs have been related with immunologic platelet destruction, like infliximab (antitumor necrosis factor-alfa antibody), rituximab (anti-CD20 antibody) or efalizumab (anti-CD11 antibody) [4]. Although rare, mild myelosuppression with trastuzumab has been reported [8]. To our knowledge, there are only two case reports published of thrombocytopenia [9].

Trastuzumab is used in patients with breast cancer with HER2 gene amplification and it has shown efficacy as single agent in metastatic breast cancer or in combination with chemotherapy [8], and in the adjuvant setting for early breast cancer [10], with an ~50% reduction in the risk of recurrence. Trastuzumab is a humanized mAb against the HER2 receptor of the breast cancer cell. Trastuzumab is produced by genetically engineered Chinese hamster ovary brown cell line on a large scale. As in the case of abciximab [11], acute thrombocytopenia after first exposure to trastuzumab would be related with preexisting antibodies specific for structural components in the trastuzumab molecule: antibody would recognize murine elements of chimeric antigen binding fragment specific for platelet membrane glycoprotein IIa [4].

In the case of drug-induced immune thrombocytopenia, once established, the diagnosis of drug sensitivity forces to avoid the medication thought to be related with thrombocytopenia. In the case of a very effective adjuvant treatment as trastuzumab, avoiding a potentially curative drug poses a special challenge. Fortunately, pharmacologic equivalents lack the potential of the original sensitizing drug [12], and it would be expected that new mAbs as pertuzumab [13] will be tolerated.

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