

Metastatic Breast Cancer with Extensive Osseous Metastasis Presenting with Symptomatic Immune Thrombocytopenic Purpura and Anemia: A Case Report and Review of the Literature

Jiaxin Niu^a Teresa Goldin^b Maurie Markman^{c, d}
Madappa N. Kundranda^a

Departments of ^aMedical Oncology and ^bPathology, Western Regional Medical Center at Cancer Treatment Centers of America, Goodyear, Ariz., and ^cDepartment of Medical Oncology, Cancer Treatment Centers of America, and ^dDrexel University College of Medicine, Philadelphia, Pa., USA

Key Words

Breast cancer · Idiopathic thrombocytopenic purpura · Anemia · Bone metastasis

Abstract

Background: Immune thrombocytopenic purpura (ITP) is a rare acquired bleeding disorder with an estimated incidence of 1 in 10,000 people in the general population. The association of ITP with breast cancer is an even rarer entity with very limited reports in the English literature. **Case Presentation:** We report a case of a 51-year-old female with no significant past medical history who presented with sudden onset of malaise, syncope, gingival bleed and epistaxis. She was found to have severe thrombocytopenia (platelet count 6,000/ μ l) and anemia (hemoglobin 7.2 g/dl). Her workup led to the diagnosis of metastatic ductal breast cancer with extensive bone metastasis. Bone marrow biopsy demonstrated myelophthisis which was initially thought to be consistent with her presentation of thrombocytopenia and anemia. Therefore, the patient was started on hormonal therapy for the treatment of her metastatic breast cancer. After 3 months of therapy, she did not improve and developed severe mucosal bleeding. Her clinical presentation was suspicious for ITP and immune-mediated anemia, and hence she was started on steroids and intravenous immunoglobulin.

The patient had a dramatic response to therapy with normalization of her platelet count and hemoglobin within 2 weeks. **Conclusion:** To our knowledge, this is the first reported case of metastatic breast cancer presenting with symptomatic ITP and anemia, and both symptoms are postulated to be immune-mediated.

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Introduction

Thrombocytopenia occurs in patients with oncological malignancies for a wide variety of reasons including bone marrow infiltration by tumor, myelosuppression by chemotherapy or radiation or peripheral platelet consumption due to disseminated intravascular coagulation or immune-mediated destruction. Immune thrombocytopenic purpura (ITP) has long been recognized to be associated with lymphoid neoplasms, particularly chronic lymphoid leukemia [1, 2]. In contrast, ITP linked with solid tumors is exceedingly rare [3]. Breast cancer is the most common malignancy in women, with an estimated 230,000 new cases predicted to be diagnosed in the United States in 2014, and accounts for roughly 30% of all new cancers [4]. To date, only 13 cases of concurrent diagnosis of breast cancer and ITP have been reported in the literature, and usually ITP is reported as mild [5–10].

We report a case of a 51-year-old woman who presented with severe thrombocytopenia and symptomatic anemia immediately preceding the diagnosis of metastatic lobular breast carcinoma with extensive bone metastases. The patient responded very well to intravenous immunoglobulin (IVIG) and high-dose steroids with normalization of both the platelet count and hemoglobin, and was able to receive further systemic therapy after 2 weeks.

Case Report

A 51-year-old perimenopausal white woman with no significant past medical history other than chronic back pain presented to her primary care physician in October 2013 with fainting spells, worsening back pain and severe fatigue of 1 month's duration. Her laboratory workup revealed a white blood count of 7,100/ μ l, hemoglobin of 8.9 g/dl and a platelet count of 60,000/ μ l, an unremarkable basic metabolic profile and normal liver function tests. Her ferritin (682 ng/ml) was elevated and both vitamin B₁₂ (392 pg/ml) and folate (20 ng/ml) levels were within normal range. The patient developed another syncopal episode at home, and an emergency room workup confirmed mild anemia and thrombocytopenia with no clear evidence of active gastrointestinal bleeding. In December 2013, due to worsening symptoms, the patient presented to a different emergency room with gingival bleeding and petechiae on her lower extremities. She was found to have a hemoglobin level of 7.2 g/dl with a platelet count of 10,000/ μ l. The patient was admitted to the hospital, and a bone marrow biopsy was performed. Bone marrow aspiration could not be obtained, and the core biopsy revealed extensive involvement of metastatic carcinoma (fig. 1b, c). Immunohistochemistry studies were highly suggestive of a breast primary (data not shown). A mammogram demonstrated a 2.4-cm mass at the 2 o'clock position in the right breast with suspicious axillary lymph nodes. The patient underwent a biopsy of both the primary breast lesion and of the axillary lymph nodes, which revealed invasive ductal carcinoma that was estrogen receptor-positive, progesterone receptor-positive and human epithelial growth factor receptor (HER2)-negative. Further staging workup demonstrated extensive osseous metastases, but no visceral metastases. She received a transfusion with 2 units of red blood cells and 1 apheresis unit of platelets, resulting in an improvement in hemoglobin from 7.2

to 10.1 g/dl and platelet count from 10,000 to 20,000/ μ l. She was discharged home and was started on endocrine therapy with both leuprolide and letrozole. Denosumab was also administered monthly for bone metastases. However, she did not respond either clinically or biochemically (rising CA 15-3) to the endocrine therapy and continued to experience frequent gum bleeds and petechial rashes throughout her body.

In March 2014, the patient transferred her care to our center. Restaging workup demonstrated extensive skeletal metastases (fig. 1a) without visceral involvement or splenomegaly (data not shown). A complete blood count showed a white blood count of 5,000/ μ l, hemoglobin of 9 g/dl and a platelet count of 10,000/ μ l. The patient received 1 unit of apheresis platelets urgently. Surprisingly, her platelet count did not increase at all, but decreased to 6,000/ μ l. The patient did not have headache, but she developed more extensive petechiae and hemorrhagic blisters in her mouth. Hence, she was admitted to the inpatient unit for further management. Both bone marrow biopsy from an outside facility and peripheral smear from our center were reviewed, and our pathologist concurred with the initial diagnosis. Peripheral blood examination of the peripheral blood smear in March 2014 revealed marked thrombocytopenia and anemia; some large platelets but no giant platelets were seen (photos are not available). There was no evidence of schistocytosis, which essentially ruled out intravascular or microangiopathic processes. It did reveal some teardrop cells, which was consistent with her bone marrow finding – a myelophthisis process. However, bone scan showed that a large fraction of long bones was spared by metastases. The disproportionate thrombocytopenia seems to suggest a dual pathological process: myelophthisis and peripheral consumption. The fact that her platelet count decreased upon platelet transfusion seems to suggest an immune-mediated peripheral destruction of platelets, which is, at least in part, responsible for her marked thrombocytopenia. All the other pertinent laboratory studies including folate, vitamin B₁₂ level, thyroid function tests, antinuclear antibodies, *Helicobacter pylori* antibodies, hepatitis panel and HIV test were normal, and therefore a clinical diagnosis of ITP was established. In view of the substantial risk of fatal bleeding, the patient received IVIG (1 g/kg) daily for 2 days (3.4.2014 to 3.5.2014) and high-dose steroid methylprednisolone 500 mg i.v. daily for 3 days (3.4.2014 to 3.7.2014). As shown in figure 2, the patient's platelet count responded dramatically, increasing from 6,000 to 32,000/ μ l in 3 days. She was discharged home with oral prednisone 80 mg (1.5 mg/kg) daily. Her platelet count improved to 155,000/ μ l 1 week later and 171,000/ μ l 2 weeks after discharge. We started to taper down her prednisone and treat her metastatic breast cancer using chemotherapy with capecitabine (500 mg p.o. daily) since she did not respond to the first-line hormonal therapy. The patient's platelet count continued to improve and was stabilized at around 250,000/ μ l. Prednisone was tapered off over 3 months, and capecitabine was gradually increased to 1,500 mg p.o. daily. Interestingly, her hemoglobin had also improved during the course of the treatment, mirroring the response of platelet count. It cannot be explained by the therapeutic response from capecitabine which was started on 3.20.2014, while her hemoglobin improved dramatically from 8.1 to 10.3 g/dl in 3 days (3.4.2014 to 3.7.2014) and further improved to 12.2 g/dl on 3.14.2014. This seems to suggest a similar immune-mediated mechanism involved in the development of anemia. By the time of completion of this report, the patient continued to respond to the current therapy with discontinuation of steroids, and the restaging CT and bone scan in September 2014 demonstrated an excellent response to capecitabine.

Discussion

ITP associated with breast cancer is extremely rare. In most reported cases, ITP was diagnosed either long before or after the diagnosis of breast cancer, suggesting the diagnosis of ITP is not necessarily secondary to breast cancer, but rather a separate coexisting condition [5, 6, 11]. Of the 10 reported cases of ITP associated with breast cancer in the largest case series, only 3 patients presented with concomitant breast cancer and ITP [7]. So far, there have been a total of 13 reported cases of concomitant diagnoses of both breast cancer and ITP; 5 cases presented with mild thrombocytopenia with a platelet count above 50,000/ μl , and 8 cases presented with severe thrombocytopenia with a platelet count $<30,000/\mu\text{l}$ [7, 9, 10, 12]. Four cases with a history of breast cancer presented with thrombocytopenia concurrently with disease recurrence (table 1). Only 1 patient presented with symptomatic thrombocytopenia (platelet count 2,000/ μl) with gingival and conjunctive bleeding resembling our case, but none of the patients presented concomitantly with symptomatic anemia [10].

The underlying mechanisms for the development of breast cancer-associated ITP are not well understood. In our case, the peripheral smear did not exhibit giant platelet as in classic ITP, but a few large platelets. Bone marrow biopsy demonstrated extensive tumor involvement, without evidence of increased megakaryocytes, which seemed to suggest myelophthisis was the only cause of thrombocytopenia. Imaging studies and normal white cell count suggested biopsy sampling error could not be excluded, and the diagnosis of ITP was made on clinical grounds of disproportionate thrombocytopenia, failure to respond to platelet transfusion and rapid response to IVIG and steroid therapy, strongly suggesting an immune-mediated mechanism in the pathogenesis. This patient also presented with symptomatic anemia, which was initially thought to be due to hemolytic anemia (Evan's syndrome). However, none of the laboratory studies (such as indirect Coombs test, normal LDH and haptoglobin) appeared to support this hypothesis. More interestingly, the rapid rise of hemoglobin paralleling the equally rapid rise of platelet count seems to suggest that the same immune-mediated mechanism might have been responsible, at least in part, for the development of anemia. In recent years, it has been increasingly recognized that peripheral antibody-coated platelet destruction is not the only mechanism behind ITP. Autoantibodies against platelets could also impair decreased production and maturation of megakaryocytes in the bone marrow [13]. It is also conceivable that autoantibodies, other than myelophthisis involving part of the bone marrow, might have impaired erythropoiesis resulting in symptomatic anemia.

There are no prospective studies or official guidelines with regard to how to manage ITP associated with breast cancer. The first challenging question to be answered is how to demonstrate the cause-effect relationship between breast cancer and ITP. Since ITP is a diagnosis of exclusion and there is no specific laboratory test to rule in the diagnosis, frequently clinicians have to treat the patient empirically based on the clinical diagnosis. In the absence of breast cancer (ITP is diagnosed before or after the diagnosis of breast cancer), it should be managed with steroids, IVIG and/or splenectomy according to standard hematology guidelines. If ITP and breast cancer are diagnosed simultaneously, then how to sequence the treatments for ITP and breast cancer becomes a complex decision-making process. The rarity of the disease precludes any prospective study. Fortunately, it seems that the overwhelming majority of the cases reported in the literature are estrogen receptor-positive breast cancer; hence, endocrine therapy becomes a safe choice, particularly in the metastatic setting. Thus, it is very reasonable to start patients with both ITP-directed therapy, such as steroids, and endocrine therapy simultaneously. If a patient had a great tumor burden or did not respond to the first-line endocrine therapy as in our case, then the time to start cytotoxic

chemotherapy would be very critical. In our case, the patient presented with symptomatic thrombocytopenia, and it is very likely that initiation of chemotherapy would have worsened the thrombocytopenia resulting in catastrophic hemorrhage. Our patient was initially treated aggressively with both IVIG and high-dose steroids followed by a slow tapering off of steroids after the patient's platelet count was normalized. Capecitabine was started overlapping with steroid therapy and, consequently, the patient was able to tolerate chemotherapy without worsening thrombocytopenia. Our case provided a successful example of sequencing ITP-directed therapy and chemotherapy in a complicated clinical scenario.

Conclusion

To the best of our knowledge, we report here the first case of a newly diagnosed metastatic breast cancer presenting with symptomatic ITP and anemia. We speculate that both symptoms, as a direct manifestation of breast cancer, were secondary to immune-mediated mechanisms. Both ITP and anemia responded well to IVIG and steroids, and the patient went on to receive further chemotherapy for her breast cancer.

Disclosure statement

None.

Statement of Ethics

None.

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Niu et al.: Metastatic Breast Cancer with Extensive Osseous Metastasis Presenting with Symptomatic Immune Thrombocytopenic Purpura and Anemia

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Table 1. Summary of reported cases of breast cancer and concomitant diagnosis of ITP

Reference, year	Patients	Concomitant diagnosis	Platelets (<30,000)	Anemia (<10 g)	Outcome
Schwartz et al. [13], 1982	1	1 (recurrence)	1	unknown	resolved
Cummings et al. [9], 1982	2	2 (recurrence)	2	unknown	resolved
Igarashi et al. [14], 1998	1	1 (recurrence)	1	normal	resolved
Porrata et al. [8], 1999	1	1	0	normal	resolved
Wahid et al. [10], 2000	1	1	1	normal	resolved
Peffault de Latour et al. [7], 2004	10	3	2	unknown	improved
Samimi et al. [12], 2010	4	4	0	normal	no therapy
Current case report	1	1	1	7.2 g	resolved

Niu et al.: Metastatic Breast Cancer with Extensive Osseous Metastasis Presenting with Symptomatic Immune Thrombocytopenic Purpura and Anemia

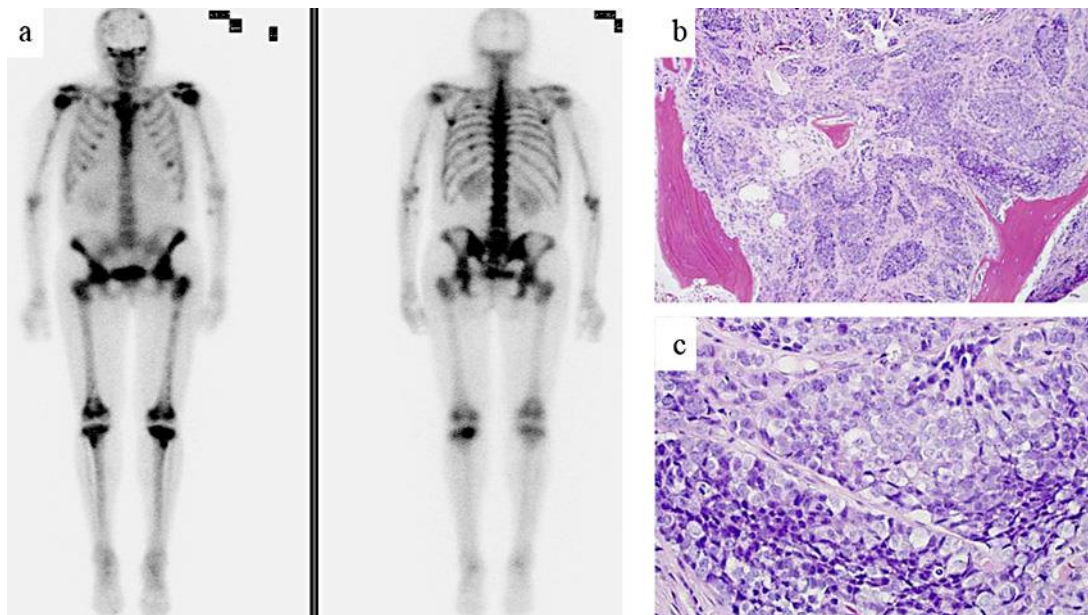


Fig. 1. **a** Nuclear medicine whole-body bone scan (March 2014). There are numerous small metastatic lesions within the skull, numerous ribs, humeri, both femurs and proximal left tibia. There is also mildly increased activity of the spine suggestive of metastatic disease. **b, c** Bone marrow core biopsy (December 2013). **b** The trabecular bone is disrupted and thinned with intertrabecular replacement of bone marrow by desmoplastic fibrosis and infiltrating sheets and angulated clusters of carcinoma cells. Magnification, $\times 100$. **c** The sheets of malignant carcinoma cells display irregular pleomorphic nuclei with irregular pale chromatin and small nucleoli and variable amounts of vacuolated cytoplasm. Abundant individual apoptotic cells and focal early necrosis are present. No gland or tubule formation is noted. Magnification, $\times 400$ (high-power view). There was no evidence of hematopoietic elements in the bone marrow core biopsy sections. Immunohistochemical stains confirmed a likely breast origin, including positivity for cytokeratin 7, cytokeratin 8/18, GCDFP-15 and estrogen receptor (data not shown). The infiltrating malignancy was identical with the invasive ductal carcinoma identified from the right breast (data not shown).

Niu et al.: Metastatic Breast Cancer with Extensive Osseous Metastasis Presenting with Symptomatic Immune Thrombocytopenic Purpura and Anemia

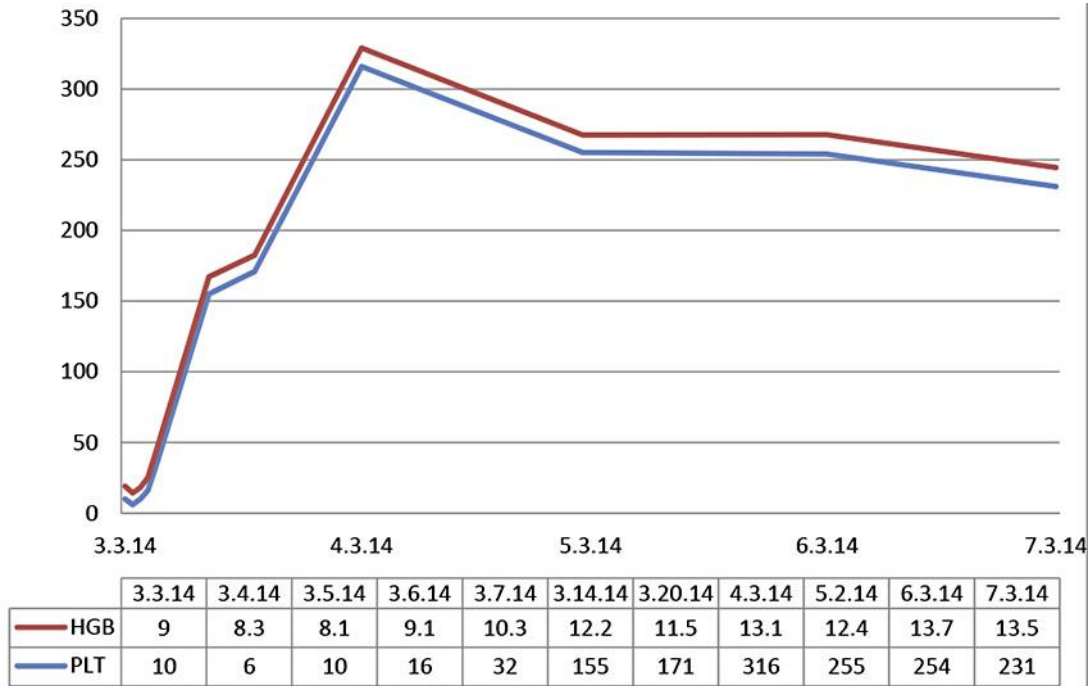


Fig. 2. Platelet count (PLT; 1,000/ μ l) and hemoglobin level (HGB; g/dl) during the course of therapy. 3.3.2014: platelet count (10,000/ μ l) and hemoglobin (9 g); 3.4.2014: the day after 1 apheresis unit of platelet transfusion; 3.4.2014–3.5.2014: the patient received 1 g/kg IVIG daily for 2 days; 3.4.2014–3.6.2014: the patient received 500 mg methylprednisolone i.v.; 3.7.2014–6.3.2014: the patient received prednisone therapy at 80 mg p.o. daily for 2 weeks, and then it was gradually tapered off until 6.18.2014; 3.20.2014: capecitabine was started at 500 mg p.o. daily and was titrated up to 1,500 mg p.o. daily on 7.3.2014.