Breast Cancer Res Treat (2014) 146:451–456
DOI 10.1007/s10549-014-3001-z

BRIEF REPORT

Ado-trastuzumab emtansine-associated telangiectasias in metastatic breast cancer: a case series

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Received: 10 May 2014 / Accepted: 13 May 2014 / Published online: 15 June 2014

Abstract Treatment of HER2-positive metastatic breast cancer with ado-trastuzumab emtansine (T-DM1), a novel antibody–drug conjugate, has resulted in both improved progression-free and overall survival. Recognition and treatment of diverse adverse events related to T-DM1 is critical for safety and tolerability. The most frequent adverse events with T-DM1 include fatigue, diarrhea, anemia, elevated transaminases, and mild-to-moderate hemorrhagic events, which are thought to be related to induced thrombocytopenia. Here, we present five case series of cutaneous and mucosal telangiectasias, definitely related to T-DM1. The development of telangiectasias represents a newly recognized adverse effect of T-DM1. We provide description and timing of the telangiectasias and review the mechanisms that may explain the formation of these vascular lesions in association with T-DM1. Further, we describe associated bleeding events and propose that induced telangiectasias could represent an additional cause of T-DM1-associated hemorrhage.

Keywords Ado-trastuzumab emtansine · Breast cancer · Hemorrhage · T-DM1 · Telangiectasia · Thrombocytopenia · Spider nevus

Abbreviations

T-DM1	Ado-trastuzumab emtansine
HHT	Hereditary hemorrhagic telangiectasia
ITP	Immune thrombocytopenia purpura
NA	Not applicable
ULN	Upper limit of normal

Introduction

T-DM1 (Kadcyla®) is an antibody–drug conjugate combining the HER2-targeted monoclonal antibody, trastuzumab, with the microtubule inhibitor mertansine (DM1). Through the combined effect of disruption of HER-2 signaling and delivery of a cytotoxic agent to HER-2 expressing cells, T-DM1 demonstrated improved

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progression-free and overall survival in patients with HER2-positive metastatic breast cancer [1–3] and is now FDA-approved for use as single agent for the treatment of these patients. The most frequently reported adverse events of T-DM1 include fatigue (35.1 %), nausea (39.2 %), diarrhea (23.3 %), elevated transaminases (16.9–22.4 %), anemia (10.4 %), thrombocytopenia (28.0 %), and hemorrhage (29.8 %), which have been attributed to thrombocytopenia [1–5]. To date, no dermatologic toxicities of T-DM1 have been reported, with the exception of mucositis and rare hand foot syndromes [3]. Herein, we describe five cases of cutaneous and mucosal telangiectasias associated with T-DM1 and hypothesize that vascular toxicity, in addition to thrombocytopenia, may predispose to T-DM1-associated hemorrhage (Table 1).

Case 1

A 66-year-old woman with stage IV breast cancer was treated with T-DM1 (3.6 mg/kg intravenous infusion every 3 weeks). Fourteen months after the initiation of treatment, the patient developed grade 2 telangiectasias of the skin with concentration on the palms (Fig. 1a). These lesions blanched with vitropressure and many were dome shaped with surrounding, small, radiating dilated vessels, akin to spider telangiectasias (Fig. 1b, c). This patient presented with multiple episodes of hemorrhage, twice requiring emergency cauterization for grade 2 epistaxis. These episodes were not attributable to thrombocytopenia as platelet counts were within normal range throughout the treatment. In addition, transaminases were slightly increased after 6 months of treatment and remained stable. Three months after discontinuation of T-DM1 secondary to non-reversible grade 3 hyperbilirubinemia, a marked regression of cutaneous lesions was observed.

Case 2

A 45-year-old woman was treated with T-DM1 (3.6 mg/kg intravenous infusion every 3 weeks) for stage IV breast cancer with liver metastasis. The first appearance of telangiectasias was noted within the first 2 months of treatment. After 3 months of treatment, she noted progressive development of telangiectasias on the trunk and palms (Fig. 2a, b). In addition, several lesions were observed on the jugal mucosa and soft palate. Fibroscopic nasopharyngeal exam did not reveal further lesions. The patient suffered grade 1, persistent epistaxis and gingival hemorrhage throughout the course of treatment. Grade 1 thrombocytopenia was observed 8 months after treatment initiation. A grade 1 increase in transaminases was also noted. Telangiectasias were persistent and stable throughout treatment, not requiring intervention.

Table 1 Summary of patients exposed to T-DM1 who developed telangiectasias

	Age (years)	Sites of metastasis	T-DM1 (mg/kg)	Additional cancer therapy	Time to presentation with telangiectasia (months)	Bleeding complications	Thrombocytopenia	Transaminitis
Patient 1	66	Brain, lung	3.6 every 3 weeks	NA	14	Multiple mucosal bleeding episodes, twice with grade 2 epistaxis	–	Grade 1
Patient 2	45	Liver	3.6 every 3 weeks	NA	3	Mild, persistent epistaxis and gingival bleeding	Grade 1	Grade 1
Patient 3	53	Liver	3.6 every 3 weeks	Pertuzumab (concurrent)	3	Limited epistaxis, occasional gum bleeding	Grade 3	Grade 1
Patient 4	43	Bone, lung, lymph nodes	3.6 every 3 weeks	Pertuzumab and paclitaxel (concurrent)	2.5	NA	–	Grade 1
Patient 5	37	Bone, brain, mediastinum, lung	3.6 every 3 weeks	Pertuzumab and paclitaxel (concurrent)	14	NA	–	Grade 1

For thrombocytopenia, platelets: grade 1 > 75,000, grade 2: 50,000–75,000, grade 3: 25,000–50,000, grade: 4 < 25,000. Transaminitis refers to elevation of aspartate aminotransferase or alanine aminotransferase above the upper limit of normal (ULN) in the reporting medical laboratory with grade 1 < ULN–3x ULN, grade 2: 3–5x ULN, grade 3: 5–20x ULN, grade 4 > 20x ULN. NA, not applicable

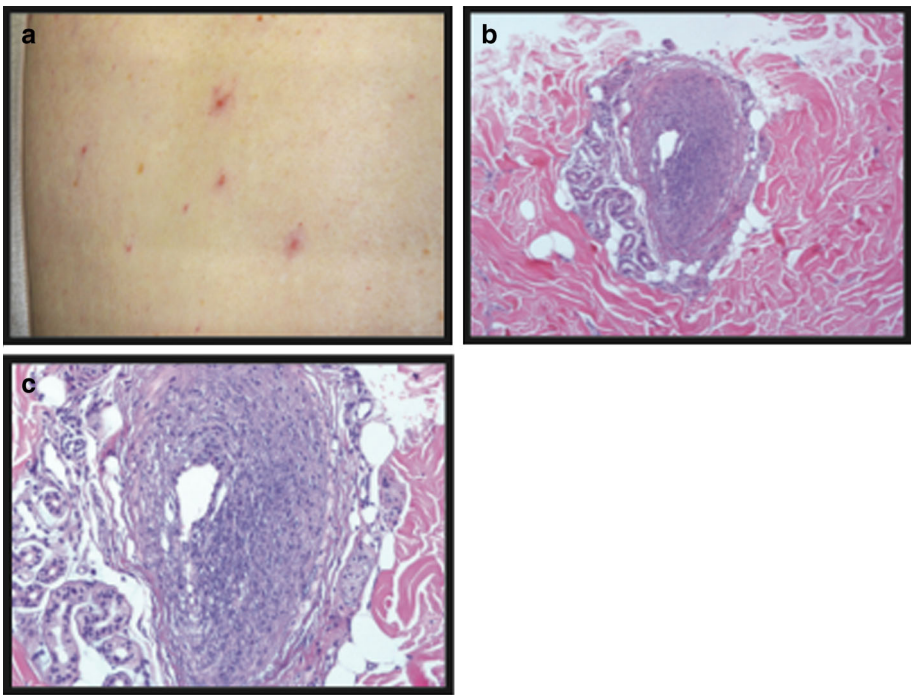

Fig. 1 Patient 1. **a** Spider telangiectasias distributed on the upper back. **b** and **c** Representative hemotoxylin and eosin staining of a biopsied telangiectatic lesion, demonstrating a central dermal vessel with intimal and medial hyperplasia, shown at 10× and 20× magnifications, respectively

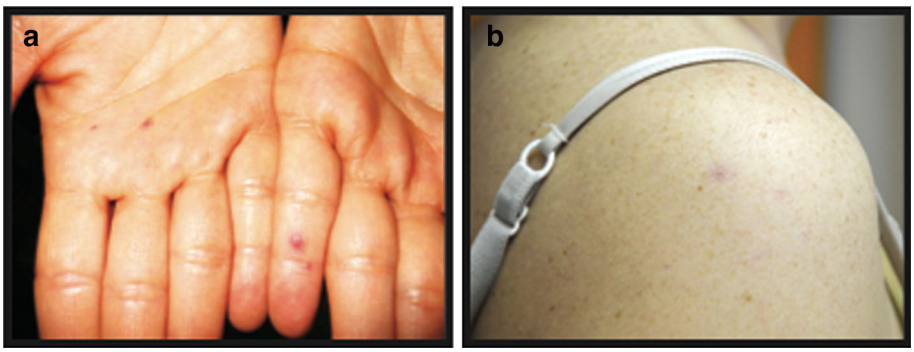

Fig. 2 Patient 2. **a** and **b** Acquired telangiectasias on the palms (**a**), and shoulder (**b**)

Case 3

A 53-year-old woman with stage IV breast cancer was treated with T-DM1 (3.6 mg/kg intravenous infusion every three weeks) plus pertuzumab as part of a clinical trial. Three months after treatment initiation, the patient noted the appearance of asymptomatic, red papules on her face, chest, and arms. Inspection revealed dome-shaped papules with halos of telangiectasias (Fig. 3a, b). The patient experienced persistent thrombocytopenia, upto grade 3 in severity, throughout treatment, requiring repeated platelet transfusions. She noted minimal, self-limited grade 1 epistaxis, and occasional gum bleeding, but did not experience hemorrhage or purpura. Dental evaluation for a fractured tooth revealed gingival erythema and edema. The patient eventually developed thrombocytopenia that was not responsive to platelet transfusions and did not resolve after withholding of T-DM1 for 2 months. This was suggestive of ongoing platelet destruction or undiscovered loss, consistent with immune thrombocytopenia purpura (ITP). Steroid pulse dosing and, later, romiplostim led to platelet recovery, supporting a diagnosis of ITP.

Case 4

A 43-year-old woman with stage IV breast cancer to the bone was treated with T-DM1 (3.6 mg/kg intravenous infusion every three weeks) plus pertuzumab and paclitaxel. After three cycles, multiple erythematous 1–2 mm papules with an erythematous halo were noted on her chest, back, and arms (Fig. 4a). These lesions were surrounded by small radiating vessels with the appearance of grade 2 telangiectasias. Biopsy revealed vascular ectasia, consistent with the clinical appearance (Fig. 4b–d). The patient

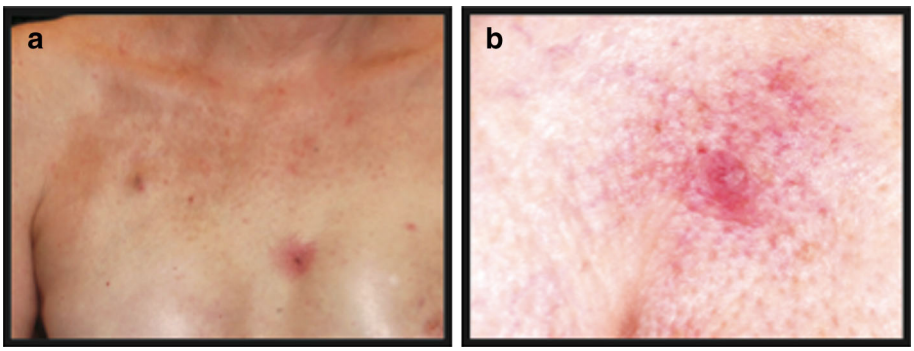

Fig. 3 Patient 3. **a** Characteristic spider telangiectasia located on the chest. **b** Vascular ectasia of the face illustrating a dome-shaped papule surrounded by telangiectatic vessels

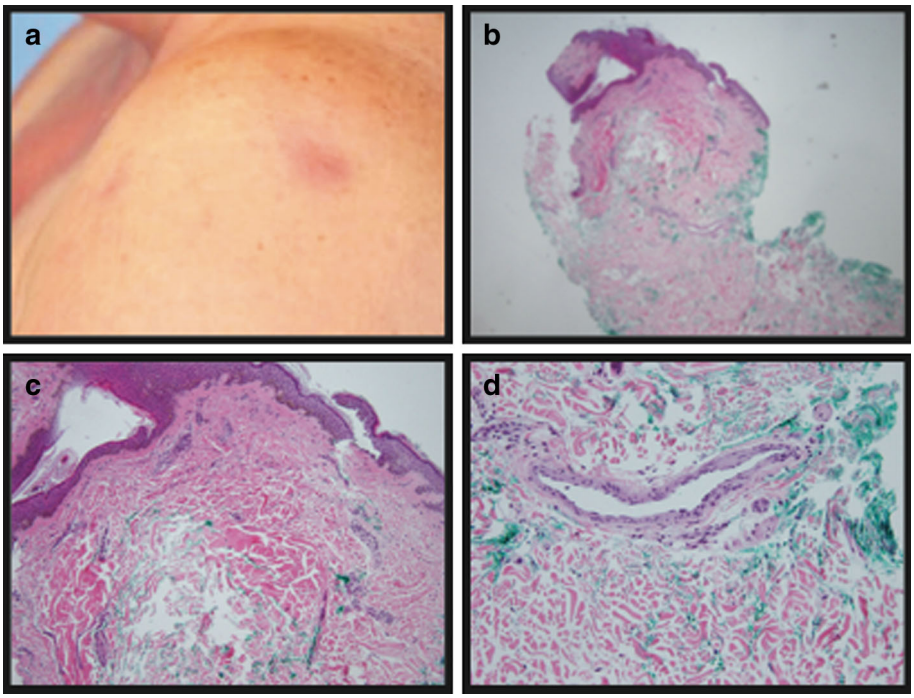

Fig. 4 Patient 4. **a** Telangiectasias on the shoulder. **b–d** Representative hematoxylin and eosin staining of a biopsied vascular ectasia, consistent with the clinical appearance of a spider telangiectasia, demonstrating a dilated central dermal vessel, shown at 2, 10, and 20×, respectively

had mild elevations in transaminases throughout treatment. She maintained platelet counts within normal range and did not report any bleeding, apart from gross blood in the urine associated with a urinary tract infection.

Case 5

A 37-year-old woman with stage IV breast cancer was treated with T-DM1 (3.6 mg/kg intravenous infusion every 3 weeks) in combination with paclitaxel and pertuzumab. Her platelets remained within normal limits. However, she experienced grade 1 elevation in transaminases throughout her T-DM1 course. She did not experience hemorrhage or purpura. Fourteen months after the initiation of T-DM1 treatment, the patient was evaluated for an acneiform rash. At this visit, multiple erythematous elevated papules on the palms, wrists, and forearms were noted, consistent with telangiectasias (Fig. 5).

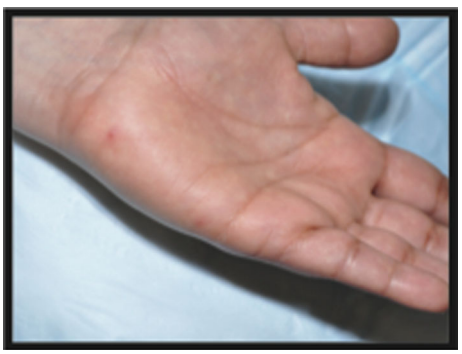

Fig. 5 Patient 5. **a** Representative telangiectasia located on the palm of patient 5

Discussion

Recognition and treatment of the diverse adverse events associated with new therapeutic options for breast cancer

remains an important component of disease management. Treatment of patients with T-DM1, a novel antibody–drug conjugate, has proven to prolong progression-free and overall survival of patients with HER2-positive stage IV breast cancer, but not without untoward events.

Here, we report five cases of cutaneous and/or mucosal telangiectasias, in association with treatment of stage IV breast cancer with T-DM1. These lesions appear, both clinically and histologically, to represent vascular ectasias. The triggering role for T-DM1 in induction of these cutaneous and mucosal lesions is supported by the temporal relationship between lesion development and T-DM1 exposure, the similarity of lesions across treated patients and the lack of other common exposures in these individuals. To date, cutaneous or mucosal telangiectasias have not been reported in association with T-DM1, trastuzumab, or emtansine.

The mechanism of mucocutaneous telangiectasia development associated with T-DM1 is unknown. Spider nevus represents a distinct type of telangiectasia characterized by a central arteriole surrounded by multiple small, radiating dilated vessels. The development of telangiectasias, specifically the spider form, has been associated with other drugs (including calcium channel blockers and lithium), autoimmune and connective tissue diseases (including lupus and systemic sclerosis), HIV infection, pregnancy, and liver damage [6]. Therefore, it is interesting to note that one of the major adverse effects of T-DM1 is liver injury with associated elevations in transaminases [1–5]. Elevation in transaminases was observed in all of the five patients herein described, although this elevation was mild.

In addition to liver damage, one may postulate a role for disruption of endothelial microtubules by emtansine in T-DM1-associated telangiectasias. Disruption of cytoskeletal microtubules has been shown to factor in the development of telangiectasias in the hereditary hemorrhagic telangiectasia (HHT) syndrome, and cytoskeletal rearrangement plays an important role in arteriole dilatation [7, 8]. While this effect has not been described in association with use of emtansine alone, it is possible that HER2 expression on endothelial cells could facilitate the trastuzumab-mediated delivery of emtansine directly to these cells, disrupting microtubules, impaired angiogenesis, and development of telangiectasias. However, HER2 is expressed at very low levels in the epidermis and skin toxicity is uncommon with trastuzumab alone [9–11]. Further, when available pathologic specimens of T-DM1-associated active telangiectasias were stained for HER2 expression, as was done for patient 4, no expression was observed in endothelial cells. Still, this does not preclude limited delivery of emtansine to endothelial cells during the initiation of telangiectasia formation, as HER2 has been found to be ubiquitously expressed in normal skin and mucosa, although at low levels [9–11]. Thus, further evaluation of mechanism is warranted.

In addition to appearing on the skin, telangiectasias can be associated with gastrointestinal, nasal, or oral mucosal involvement. The presence of telangiectasias has been linked to hemorrhages, as described in HHT [12]. Telangiectasias in HHT, a disease associated with mutations in genes in the transforming growth factor β-signaling pathway, are attributed to an imbalance of pro- and anti-angiogenic factors, producing friable and dilated vascular endothelium with a tendency for hemorrhage. In this context, the description of induced vascular lesions associated with T-DM1 may be more than anecdotal. We hypothesize that telangiectasias observed following treatment with T-DM1 may contribute to the mucosal bleeding observed in association with T-DM1 exposure. While this complication has been largely attributed to the documented impact of T-DM1 on platelet synthesis, hemorrhage in the absence of thrombocytopenia or with only mild thrombocytopenia (grade 1) is herein described and has been reported elsewhere, with gastrointestinal hemorrhage and epistaxis occurring in exposed patients with normal platelet numbers [3, 13]. In addition, these telangiectasias may lead to greater extent of hemorrhage when thrombocytopenia is present.

Thus, we describe a novel association between T-DM1 exposure and mucocutaneous telangiectasias, which may factor importantly in the adverse bleeding events associated with the use of this agent for patients with HER2-positive metastatic breast carcinoma. This observation suggests the need for a prospective evaluation of patients treated with T-DM1, for better characterization visible telangiectasias at the epidemiological, clinical, and anatomopathological levels.

Acknowledgments We express our gratitude to the patients and staff at Memorial Sloan Kettering Cancer Center and the Cancer University Institute. REN was supported by a Medical Scientist Training Program grant from the National Institute of General Medical Sciences of the National Institutes of Health under award number T32GM007739 to the Weill Cornell/Rockefeller/Sloan-Kettering Tri-Institutional MD PhD Program.

Conflict of interest VS, REN, KS, HR, and JPD declare that they have no conflicts of interest. SM received funding from Genentech for research. MEL has a speaking, consultant, or advisory role with Advancell, AstraZeneca, Aveo, Bayer, Berg Pharma, Bristol-Myers Squibb, Galderma, Genentech, Genzyme, GlaxoSmithKline, Helsinn, Imclone, Lilly, Lindi Skin, Merck, Novocure, Onyx, Pfizer, Roche, Sandoz, Sanofi Aventis, and Wyeth. The authors declare no financial relationship with a sponsoring institution.

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