Paraneoplastic cutaneous small-vessel vasculitis as a presentation of recurrent metastatic breast cancer

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INTRODUCTION

Cutaneous small-vessel vasculitis (CSVV) is a vasculitis of small vessels that classically presents with purpuric papules on the lower extremities. It may occur in the setting of several triggers such as infection, drug exposure, and collagen vascular disease.[1] Of all cases of CSVV, fewer than 5% are thought to be paraneoplastic.[2] Most of these cases are associated with hematologic malignancies (90%), whereas the remainder are associated with solid organ malignancies (10%).[3] We present a rare case of paraneoplastic CSVV that specifically occurred in the setting of recurrent metastatic breast cancer.

Abbreviations used:

CSVV: cutaneous small-vessel vasculitis

CASE REPORT

A 53-year-old South African woman presented to our dermatology department with a 2-week history of painful skin lesions on the arms, legs, and trunk. She denied using any medications in the recent past. There was no recent history of fever or symptoms of multiorgan involvement such as arthritis, abdominal pain, melena, hematuria, hemoptysis, or headaches. Stage IIB infiltrating ductal carcinoma of the left breast with left axillary lymph node metastases was diagnosed 11 months previously. She was not placed on a selective estrogen receptor modulator because immunohistochemistry showed negative staining for the estrogen and progesterone receptors. She underwent a modified radical mastectomy followed by 6 cycles of adjuvant chemotherapy. She received 3 cycles of doxorubicin and cyclophosphamide and 3 cycles of paclitaxel. She had also received radiotherapy.

The physical examination found palpable purpura with associated necrosis, bullae, and well-delineated ulcers on both the upper and lower limbs as well as the trunk (Fig 1). The general and systemic examination were normal. There was no lymphadenopathy or features suggestive of infection.

Histology of the skin punch biopsy showed full-thickness epidermal necrosis and ulceration with superficial blister formation (Fig 2). In the dermis, there was severe perivascular neutrophilic inflammation, nuclear debris, fibrinoid necrosis of the vessel walls, and erythrocyte extravasation (Fig 3). Periodic acid–Schiff and Grocott (silver stain) were negative for fungal yeasts and hyphae. Brown and Brenn was negative for bacterial organisms. Martius Scarlet Blue was negative for fibrin thrombi. Immunofluorescence studies (IgA, IgG, IgM, and C3) were negative in the basement membrane and perivascular regions. The features were consistent with leukocytoclastic vasculitis.

Initial laboratory findings showed a mild normocytic anemia on full blood count. Serum alkaline phosphatase levels were 182 U/L (normal range, 42–98 U/L). The antistreptolysin O and anti-DNase B

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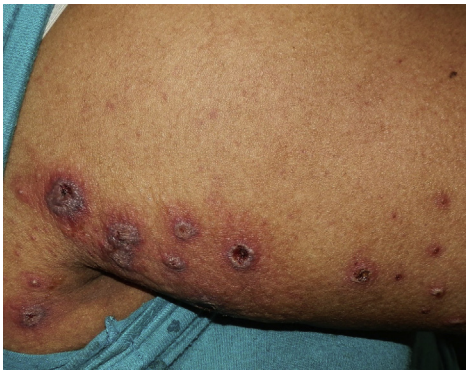

Fig 1. The upper arm displays palpable purpura with associated necrosis, well-delineated ulcers, and bullae.

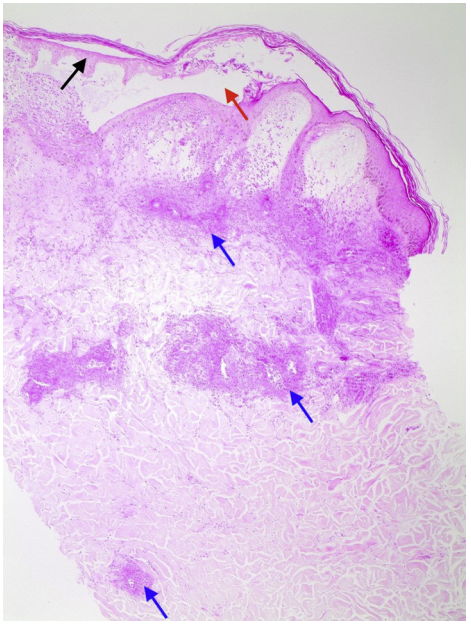

Fig 2. Histopathology. A low-power view of the skin punch biopsy shows epidermal necrosis (black arrow), blister formation (red arrow), and leukocytoclastic vasculitis (blue arrow) involving the dermal blood vessels. (Hematoxylin-eosin stain; original magnification: x2.)

titers were within normal limits, and the viral hepatitis panel was negative. Tests for antinuclear antibody, rheumatoid factor, and antineutrophil cytoplasmic antibody were all negative. Serum creatinine was normal, as was urinalysis. Chest radiograph and abdominal ultrasound scan found no abnormalities. Bone scintigraphy with technetium 99m-methylene diphosphonate was suspicious for skeletal metastases, showing abnormal increased uptake in the first thoracic vertebrae and right ninth rib.

A diagnosis of recurrent metastatic breast cancer with paraneoplastic cutaneous CSVV was made after excluding other causes of CSVV. Treatment consisted of supportive care and local wound care. Oral dapsone, 100 mg daily, was also started based on severity of skin involvement. Her skin lesions improved gradually, and she had no further episodes of vasculitis. She was discharged and referred to the oncology department for further treatment. Despite further treatment with chemotherapy, she presented to the emergency department 6 months later with recent-onset headaches and vomiting. She also had an ataxic gait. Magnetic resonance imaging of the brain found a solitary left cerebellar lesion. A posterior fossa craniotomy was performed with resection of the lesion. Histopathology of a specimen obtained during surgery was consistent with metastatic adenocarcinoma. Immunohistochemistry for estrogen and progesterone receptors were negative and *HER2* was strongly positive, matching the immunohistochemical profile of the original mastectomy specimen. The GATA-3 positivity also favored a metastatic adenocarcinoma of primary breast origin. She is due to receive further radiotherapy for palliation.

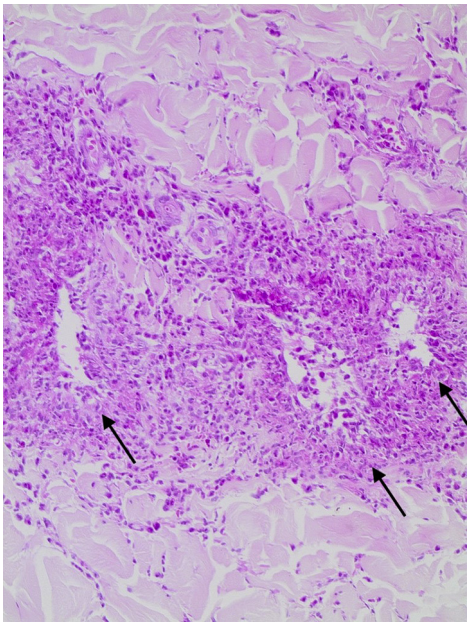

Fig 3. Histopathology. A medium-power view of the dermal blood vessels with marked neutrophilic perivascular inflammation (black arrows). (Hematoxylin-eosin stain; original magnification: x10.)

DISCUSSION

CSVV is a vasculitis of the small vessels that features leukocytoclasis of infiltrating neutrophils with fibrinoid necrosis of the vessel wall and associated erythrocyte extravasation.[2] In our case, the vasculitis was likely a paraneoplastic phenomenon associated with recurrence of our patient's

malignancy for 2 reasons: (1) the CSVV developed in parallel with the diagnosis of tumor recurrence, and (2) no other cause could be found after thorough investigation.

We performed a search of Pubmed, Scopus, and Web of Science using MeSH terms and title/abstract keywords for case reports and other studies related to CSVV and breast cancer. Several case reports of CSVV in breast cancer were related to chemotherapy or hormonal therapy, such as aromatase inhibitors.[4-7] We found 1 case report of recurrent metastatic breast cancer presenting as paraneoplastic cutaneous vasculitis.[8] However, the vasculitis was likely antineutrophil cytoplasmic antibody associated. Moreover, the authors were unable to differentiate between paraneoplastic and drug-induced vasculitis. Another case report of paraneoplastic CSVV was related to primary breast cancer, but not metastases or recurrence.[9] Furthermore, the authors of a retrospective chart review of solid organ malignancy in CSVV described 3 cases of breast cancer associated with CSVV.[10] However, cases were not specifically related to recurrent metastatic breast cancer.

The pathophysiologic mechanisms underlying paraneoplastic CSVV remain unclear. It is thought that tumor antigens released into the circulation lead to the formation of immune complexes, which deposit in small vessels.[2,10] Complement fixation follows with attraction and activation of neutrophils, resulting in the release of lytic enzymes. In addition to those in the skin, the small vessels of the gastrointestinal and renal systems may rarely be involved.[2] The time between onset of vasculitis and diagnosis of malignancy is also variable. Vasculitis may present before, during, or after diagnosis of malignancy.[10]

Although we present a unique association of paraneoplastic CSVV, our case also has important educational value. In cases of CSVV with no apparent cause, we recommend that physicians make a thorough search for a new malignancy in a previously cancer-free individual or for tumor recurrence in a patient with a history of malignancy.

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