Case Report

Cutaneous and Gastrointestinal Leukocytoclastic Vasculitis Induced by Palbociclib in a Metastatic Breast Cancer Patient: A Case Report

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Clinical Practice Points

- The efficacy and safety of palbociclib, a cyclin-dependent kinase 4/6 inhibitor, used in combination with fulvestrant was assessed in women with advanced breast cancer (ABC) whose disease had progressed during previous endocrine therapy, with a significant improvement of progression-free survival and good health-related quality of life.
- We report a case of an 80-year-old patient with ABC who presented a cutaneous and gastrointestinal vasculitis during treatment with palbociclib and fulvestrant.
- The skin biopsy was consistent with a leukocytoclastic vasculitis with immunoglobulin A deposits in dermal blood vessels. The symptoms disappeared with the arrest of palbociclib and fulvestrant treatment and a high dose corticotherapy.

Clinical Breast Cancer, Vol. ■, No. ■, ■-■
Keywords: Cyclin-dependent kinase 4/6 inhibitor, Drug-induced vasculitis, Faslodex, Fulvestrant, Ibrance, Vasculitis treatment

Introduction

Vasculitis includes a wide spectrum of diseases with diverse etiologies. All of them share a small blood vessel inflammation mechanism.[1,2] Drug-associated vasculitis represents approximately 20% of all etiologies.[3]

Palbociclib, a cyclin-dependent kinase 4/6 inhibitor, combined with fulvestrant, showed a significant improvement of progression-free survival, for patients with estrogen receptor-positive (ER^+)/$HER2^-$ advanced breast cancer resistant to previous endocrine therapy in the multicentre, double-blind, phase 3 randomised controlled trial PALOMA 3.[4] Recently, palbociclib received accelerated approval as a first-line of treatment in combination with the aromatase inhibitor, with a maintained health-related quality of life.[5,6] To our knowledge, no leukocytoclastic vasculitis has been reported either in the PALOMA trials, or with other CDK 4/6 inhibitors, ribociclib and abemaciclib.[7,8] To our knowledge, we report the first potential case of a leukocytoclastic vasculitis that might be induced by a CDK 4/6 inhibitor: palbociclib. It seems relevant to improve our knowledge and management of side effects of this drug, not reported in clinical trials.

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Submitted: May 18, 2018; Accepted: Jul 3, 2018

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Case

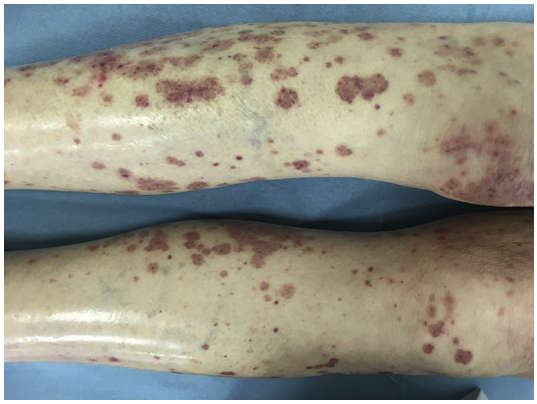
In 1992, an 80-year-old Caucasian woman presented a breast lobular carcinoma ER^+/$HER2^-$, at an early stage, treated with lumpectomy, cobaltotherapy, and tamoxifen for 3 years. In 2011, a local and oligometastatic relapse was diagnosed with an isolated bone thoracic metastasis. A mastectomy was performed, followed by hormonal therapy (letrozole) and bisphosphonates. Because of arthralgias, letrozole was switched to exemestane in 2013. She stopped the endocrine therapy in March 2015 by herself for the same reason. Bisphosphonate treatment was continued for only 1 year.

Medical history of this patient includes Biermer disease diagnosed in 1999, an appendectomy, a pulmonary embolism secondary to the breast surgery in 1992 treated with kardegic, and neuropathic pain treated with gabapentin.

In December 2016, the patient consulted for a dyspnea caused by a left pleurisy observed on the computed tomography (CT) scan. A talc pleurodesis was performed and presence of ER^+ breast cancer cells (cytologic prelevement) in the pleural liquid confirmed the metastatic relapse. We started a second line of hormonal therapy

1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2018.07.006

Figure 1 Petechial and Palpable Purpura of the Lower Limbs



combining fulvestrant with palbociclib as recommended. She received palbociclib (Ibrance; Pfizer, Mission, KS) with a reduced dose, 100 mg per day, on 21 days of 28, because of her advanced age associated with fulvestrant (Faslodex; AstraZeneca, Wilmington, DE) 500 mg using intramuscular administration, bimonthly the first month and then monthly. The treatment started on February 7, 2017. During the first month of treatment, the patient only described a 3-day fever, around 38°C starting on the 21st day. She received a probabilistic antibiotherapy without neutropenia (polynuclear cell count was 1470/mm^3). During the beginning of the second cycle, she described the same fever relapse on day 21 with lower limbs eruption. Clinical examination revealed an infiltrated purpura with petechiae on the edematous lower limbs (Figure 1). Despite the cutaneous symptoms, the treatment was well tolerated with only Grade 1 diarrhea and vomiting and no neutropenia (the main side effect of palbociclib). Doppler ultrasound exam did not show any thrombosis. Palbociclib and fulvestrant were immediately stopped and the patient was referred to a dermatology department, for investigation and treatment.

A skin biopsy was consistent with a leukocytoclastic vasculitis (Figure 2), with antibody deposit revealed in positive immunofluorescence analysis. Blood cell count showed 5000/mm^3 polynuclear neutrophilic cells, 517,000/mm^3 platelets, and 107 g/L of hemoglobin, without hepatic or ionic disorder. Initially, the C-reactive protein count was 162 mg/mL and erythrocyte sedimentation rate was increased (49 seconds). Coagulation tests showed prothrombin time was 80%, fibrinogen and D-dimer were elevated respectively at 5.88 g/L and 6800 ng/mL. Blood tests were negative for antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies, cryoglobulins, antiphospholipid antibodies, anti-glomerular basement membrane antibodies, and hepatitis B and C virus serology. The complement-fixation test was normal. Urinary examination showed a mild (0.32 g per day) proteinuria and was sterile.

The skin eruption was increasing to upper limbs and trunk with petechiae, and hemorrhagic and necrotic vesicles. Three weeks after the skin signs began, she presented lower gastrointestinal bleeding and diarrhea. The abdominal CT scan showed bowel fat thickening of the third duodenal portion and of the first jejunum portion, associated with moderate ascites and bowel dilatation. The patient's stool culture and *Clostridium difficile* research were negative and confirmed the suspected gastrointestinal vasculitis. The patient was initially treated with colchicine 0.5 mg twice a day for 4 days, then with prednisone 1 mg/kg/day when gastrointestinal signs appeared. Low molecular-weight heparin treatment was started. Bleeding and purpura regressed at approximately 3 days after the beginning of corticotherapy, allowing gradual reduction of the prednisone dose, quickly followed by hydrocortisone. The C-reactive protein also decreased to normal level. One month later, tamoxifen was introduced instead of fulvestrant, because of the low accountability of fulvestrant. Three months later, cutaneous examinations have gone back to normal. As of February 2018, the patient was still undergoing tamoxifen treatment, and presented a stable disease, well safety, and has never complained about new gastrointestinal or skin symptoms.

Discussion

Skin signs in our patient were comparable with other descriptions in the literature. A vascular purpura, on dependent areas, sometimes associated with swelling of the leg are common.[2,3,9] Fever is also described as prodrome and might be because of immune reaction or pre-exposure effect of drugs. In this case, the presence of nuclear dust, fibrinoid necrosis, and blood vessel inflammatory infiltration were consistent with leukocytoclastic vasculitis. The negative rate of ANCA, the type A antibody deposits in the dermal vessels, and the

Figure 2 Immunofluorescence Microscopy of Skin Biopsy. IgA Deposit on the Left Side and C3 Deposit on the Right Side