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Research Article

A Case Report of Hormon Positive Breast Cancer with Early Relapse and Adverse Event on CDK4/6 Inhibitor

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Abstract

Introduction: *Hormon positive breast cancer is the most common breast cancer worldwide, with estrogen and progesterone receptor positivity, and Her 2 negative. Prognosis for patients with this kind of breast cancer biology is slightly better than the other types because of possibility of adjuvant endocrine therapy that reduces the risk of recurrence by approximately 50% and improves the survival of these patients.*

Case Report: *Physical exam of our 60 year old patient revealed an irregular, hard lump of around 30x40mm at the junction of the upper quadrants of the right breast. In the right axilla, there was one palpable lymph node about 20x20mm in size. Breast ultrasound and mammography confirmed the same. Breast CORE biopsy was performed and patology report was: invasive ductal breast cancer, G3, ER 8, PgR 0, Her2 2+ without gene amplification, Ki67 35%. Initial CT of chest, abdomen and pelvis and bones scintigraphy showed no disease dissemination. We started chemotherapy, AC for IV cycles, than Docetaxel for IV cycles, after which we have progression in axilla, lymph node of 22mm. MDT decided that patient is going to undergo surgery, right mastectomy with axillary dissection. Pathology report was: invasive and in situ ductal breast cancer, G3, ypT3N2, ER 8, PgR 0, Her2 0, Ki67 30%. Patient completed radiotherapy in June 2021 and was on adjuvant anastrozol. In December 2022 there was disease progression, chest CT reveales in S3 and S6 of left pulmonary lobe two subpleural masses 13 and 6 mm, with radiological features of secondary deposits, so MDT decides that patient will start first line treatment for metastatic hormone receptor positive breast cancer with examestane and ribociclib. After two weeks of therapy patient reports macular rash on upper extremities, chest and back. Both drugs were stopped, and patient was given symptomatic therapy and after the rash completely disappeared she continued the therapy. On fourth cycle of ribociclib, rash reappeared on lower extremities, both drugs were stopped and patient was sent to test for allergic reactions to both drugs. With tests, the existence of hypersensitivity to the tested drugs was not established.*

The MTD with the dermatologist concluded that this is either skin toxicity of ribociclib or acetylsalicylic acid (ASA)-mediated urticaria because the patient was taking this drug without our prior knowledge. On control CT findings in May 2023 partial response is confirmed and it has been decided that patient continues with previous treatment, now with reduced doses of ribociclib.

Conclusion: *Cyclin-dependant kinase 4 and 6 inhibitors have multiple adverse events, and skin toxicity is one of them, mostly found to be very rare. Nevertheless, it affects patients quality of life and could lead to treatment discontinuation, which is why recognizing and managment of it is very important.*

Key words: *early relapse of hormone positive breast cancer; CDK4/6 inhibitors; skin toxicity.*

Introduction

Breast cancer is one of the most commonly diagnosed cancer types among females, with an estimated 2.3 million new cases (11.7%), and 685.000 deaths in 2020 (1). There are three major subtypes of breast cancer, depending on the expression of three tumor markers: estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor 2–neu (Her2). The most common subtype is hormone receptor positive (ER or PgR), encompassing the luminal A and luminal B subtypes. Luminal B cancers, HER2 overexpressing tumors, and triple-negative breast cancer have a poor prognosis because they are more clinically aggressive (2). Hormone receptor-positive breast cancer represents approximately 75% of breast cancers (3). Patients with ER-positive breast cancers have relatively better survival compared to those with the other subtypes. The rationale for improved survival is that these patients respond to endocrine therapy, which is used in several settings, including neoadjuvant, adjuvant, as well as metastatic breast cancer. Adjuvant endocrine therapy reduces the risk of recurrence by approximately 50%, and improves the survival of these patients (4).

Case Presentation

The patient is female, 60 years old at the moment of diagnosis. Two months before the visit to our ambulance she felt a lump in her right breast. Physical exam reveals an irregular, hard lump of around 30x40mm at the junction of the upper quadrants of the right breast, with no skin and chest involvement. In the right axilla,

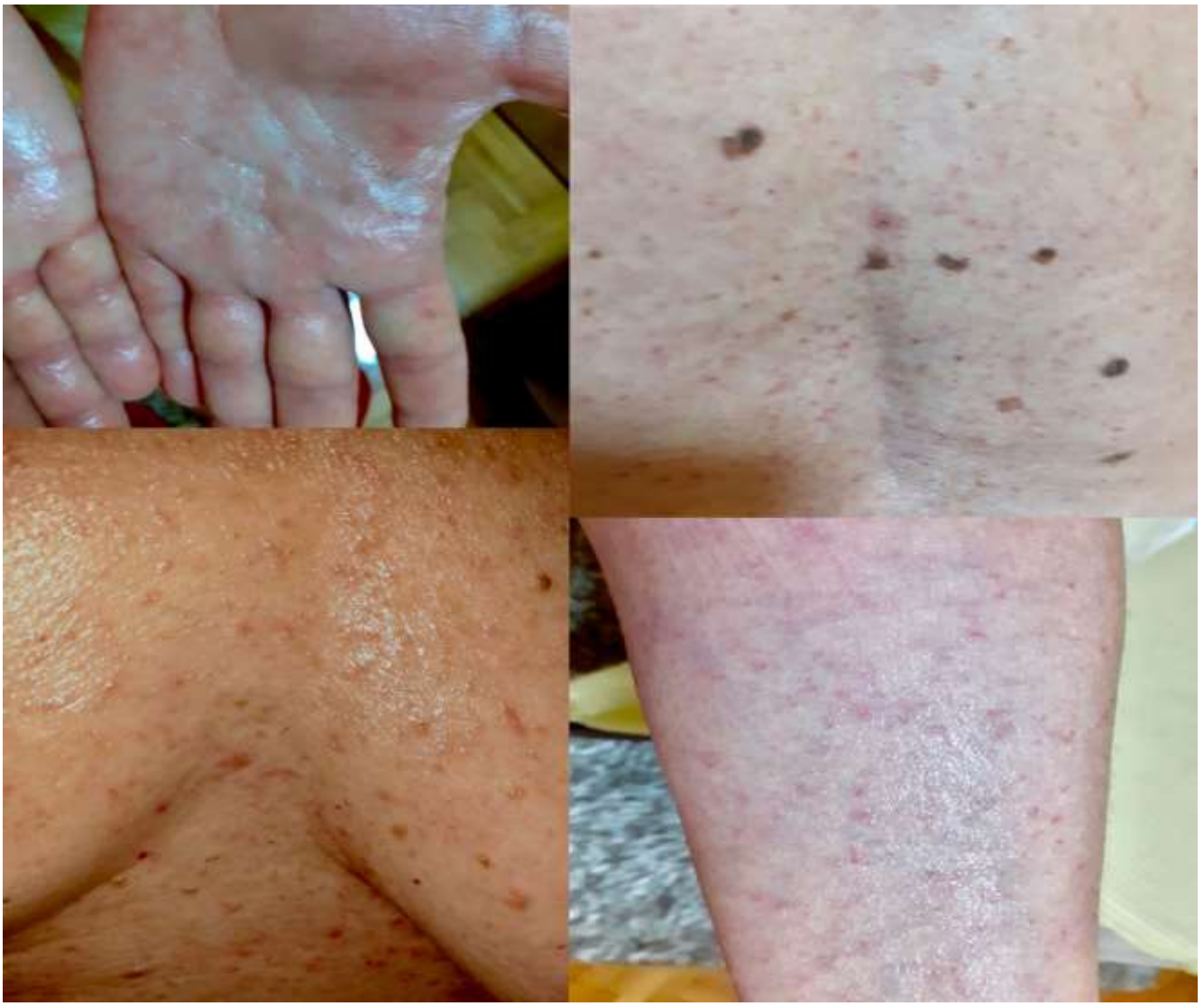
there was one palpable lymph node about 20x20mm in size. Breast ultrasound and mammography confirmed the same: in the junction of upper quadrants an irregular mass, 28x20mm in size with microcalcifications, and in right axilla enlarged lymph nodes with diameter of 18mm. Patient was a heavy smoker, had no prior comorbidities, negative familial history of malignancies. A breast CORE biopsy was performed which showed invasive ductal breast cancer, G3, ER 8, PgR 0, Her2 2+, without gene amplification, Ki67 35%. Initial CT of chest, abdomen, and pelvis, and bone scintigraphy shows no disease dissemination. Multidisciplinary tumor board **(**MDT**)** decides to go for neoadjuvant anthracycline-based chemotherapy. We started chemotherapy in November 2020, and after four cycles of AC protocol, clinical and radiological findings showed slight regression. The patient continued neoadjuvant chemotherapy with four cycles of Docetaxel. After completing neoadjuvant chemotherapy we have stabile disease in the breast, but on ultrasound we see slight progression in the size of the lymph node in the right axilla, which now measures 22x22mm. After ruling out the preasence of metastatic disease with CT scans, MDT decided that the patient is going to undergo surgery, right mastectomy with axillary dissection. A pathology report is in favor of bad therapeutic response: invasive and in situ ductal breast cancer, G3, ypT3N2, ER 8, PgR 0, Her2 0, Ki67 30%. The patient completed radiotherapy in June 2021 and was on adjuvant anastrozole and a regimen of regular quarterly controls.

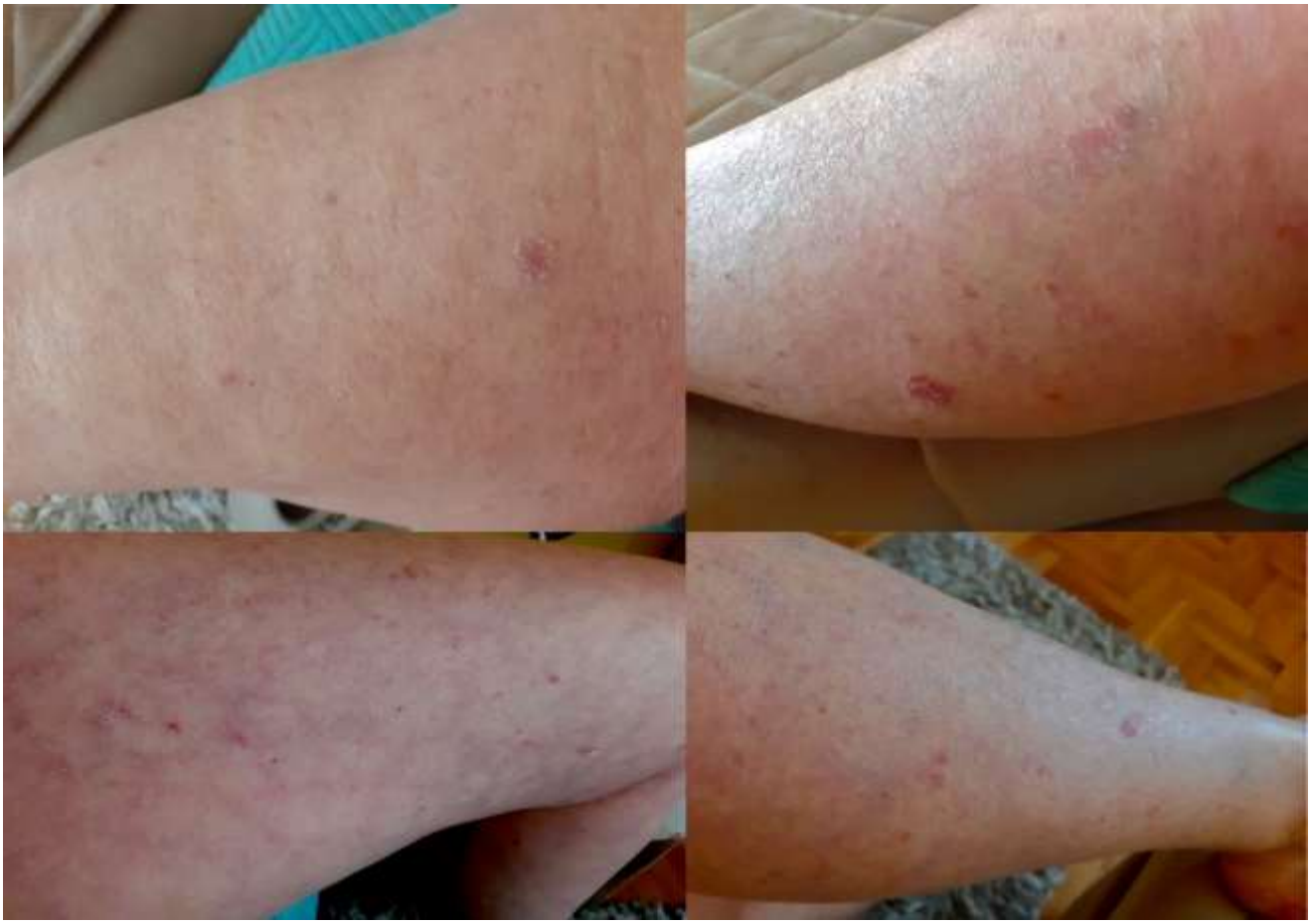
In December 2022 CT chest, abdomen, and pelvis, bone scan, and a complete laboratory were done. At that time patient was for 18 months on adjuvant endocrine therapy. Chest CT showed in S3 and S6 of the left pulmonary lobe two subpleural masses 13 and 6 mm, respectively, with radiological features of secondary deposits. The patient started first-line treatment for metastatic hormone receptor-positive breast cancer with exemestane and ribociclib. After two weeks of therapy, in January 2023, the patient reports maculopapular rash on upper extremities, chest, and back, accompanied by itching and a burning sensation **(**Figure 1**)**. Both drugs were stopped, and the patient was given systemic and topical therapy with corticosteroids, and systemic antihistamines. After the rash completely disappeared, a new cycle of therapy was started. The patient came to us one or two times monthly and had no complaints. Complete blood count and liver functioning test are usually within normal range, grade II neutropenia was seen only in first three cycles.

On the fourth cycle of ribociclib, in May 2023, the rash reappeared on the lower extremities **(**Figure 2**)**. This time only ribociclib was stopped, and supportive therapy was added, but the rash wasn't gone, so we stopped both drugs and referred the patient to test for allergic reactions to both drugs. During the testing, the patient was without any treatment for about one month. With allergological testing in vitro and in vivo, with

epicutaneous and scarification tests, the existence of hypersensitivity to the tested drugs was not established. The MTD with the dermatologist concluded that this is either skin toxicity of ribociclib or acetylsalicylic acid **(**ASA**)**-mediated urticaria because the patient was taking this drug without our prior knowledge. There are no known interactions between ASA and ribociclib and/or exemestane.

On control CT findings in May 2023, a partial response is confirmed: subpleural nodular lesion in the S3 of the left lung was reduced in size in comparison with the CT finding from December 2022, subpleural lesion in S6 of the left lung wing was stationary in size. The decision made on MDT was that the patient continues the previous treatment with reduced doses of ribociclib, and stop or change antiplatelet therapy. Now, for three months patient did not have any more side effects. If the rash reappears the plan is to switch to another cyclin-dependant kinase 4 and 6 inhibitor **(**CDK4/6**)**, palbociclib.





Discussion

In this case, according to the definition, we have a patient with primary endocrine resistance, because the relapse occurred within the first two years of adjuvant endocrine therapy. Mechanisms of endocrine resistance include aberrations in the ER/PgR/androgen receptor **(**AR**)**, genomic and epigenetic alterations of ERS1, expression of truncated ER-isoforms, post-translational modification, increased receptor tyrosine kinase signaling, altered cell cycle regulation, somatic alterations, tumor microenvironment **(**5,6**)**. Due to the multiple possibilities of endocrine resistance, it is of great importance to develop optimal combinations in treatment and sequencing strategies. Even in endocrine-resistant breast cancer, the ER remains a promising target. This is why next-generation more selective estrogen receptor downregulators **(**SERDs**)** with enhanced bioavailability are under investigation. It is shown that CDK4/6, mTOR, and PI3K inhibition can enhance the efficacy of endocrine treatment, and novel promising drugs that target further components of key pathways like the PI3K/AKT/mTOR pathway are currently being developed **(**7**)**.

The landscape of treating HR+ breast cancer has been changed after PALOMA 1, MONALEESA 2, and MONARCH 3 studies, after which palbociclib, ribociclib, and abemaciclib were approved for first-line treatment of advanced HR+/Her2- breast cancer in postmenopausal women, respectively (8). Although CDK4/6 inhibitors demonstrate promising efficacy, their unique mechanism of action is also associated with numerous toxicities. Different cutaneous side effects have been reported. Sumir Chawla et al. found the incidence of treatment-related cutaneous adverse events (AE) was in 46 from a total of 324 patients (14.2%) The most frequent cutaneous reactions included maculopapular rash (41%), asteatosis (37%), pruritus and urticaria (20%), and bullous dermatitis reactions (9%). In their study patient received at least 9 cycles of palbociclib, which was not the case in our patient who developed the first skin reaction during the first cycle (9). In a meta-analysis by Costa et al. from 2017, rash was found to be a very rare adverse event with absolute risk being 0.17 for any grade AE (CI 95% 0.15, 0.19) (10). Elena Fountzilas et al. investigated adverse events in 363 patients from their study and found that skin AE of grades 1 and 2 was in 5 patients (1.4%), while there were no higher grades of skin disorders (11).

Conclusion

In the Republic of Serbia, we use CDK4/6 inhibitors for more than a year now. Real-world data on AE are of great importance for clinicians in terms of recognizing and adequately managing them. Skin toxicity is an important issue, and most often, it is not life-threatening, but it affects a patient's quality of life and could lead to a discontinuation of therapy, and that is what we have to avoid.

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